I N D E X

December 9, 1999

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Keynote: --- indicates inaudible in transcript.

M O R N I N G S E S S I O N

(8:45 a.m.)

WELCOME AND OUTLINE OF SCOPE, PURPOSE AND OBJECTIVES OF WORKSHOP

Dr. Stephen Sundlof

DR. SUNDLOF: My name is Steve Sundlof and I am the Director of FDA's Center for Veterinary Medicine. And it is my pleasure to be able to host this meeting. Before we get started, just a little bit of background as to where this meeting fits into the grand scheme of things.

Back in January of 1999, we held a Veterinary Medicine Advisory Committee. And at that committee, we discussed a document which we referred to as the Framework Document -- I think there are copies out on the table of that document -- which basically described the Agency's best thinking at that time as to what might be a rational approach to regulating antimicrobials as it pertains to the human food safety aspects of antimicrobial resistance.

And at that meeting, we said that there would be additional workshops to discuss specific issues, specific parts of that framework. And this is one of those meetings. And since the meeting in January, we have put in a great deal of effort, listened to a lot of what people had to say, read through many, many comments and tried to respond accordingly.

So today is the continuation of that process. And, as you might guess, it will not be the end. There will be additional meetings that will be held. I would like to start off with just a few philosophical points. And these are my own philosophical statements, but to try and set the tone for the meeting for the next two days.

(Laughter.)

We don't have to worry about OSHA I am sure.

(Laughter.)

FDA as an agency is a science-based, public health, regulatory agency. It has all those three things. It is science-based. It is decisions. And it is regulations. By law, I have to be based in science. It is a public health agency and a consumer protection agency.

And it is also a regulatory agency. We do have the authority to take regulatory actions to support the decisions that we make.

I want to talk about the science part of it. It is very important to FDA and I think to society at large that our policies and our regulations are supported by the body of science as it is known at the time and at the same time, recognizing that there will always be uncertainties in that body of science.

The scientific method is by design contentious -- well, it is a messy process. It involves intense debate, critical scrutiny of underlying assumptions, experimental designs and interpretations of results. At times, it can become contentious and acrimonious. And for many people, it can become an uncomfortable event. But that is part of the scientific process. And in many cases, it is only through that emotionally charged process that science advances.

It is therefore important that we allow that process to play out and that we resist the temptation to cut off the debate prematurely. I am hopeful in the next two days that we will contribute positively to that debate. And that is my sincere hope for this meeting.

To help set the tone for the next two days, I would like to make a proposition with all of you. We at FDA will make a concerted effort to listen to you if you can all agree to listen to each other.

That doesn't mean that we shouldn't challenge one another to support his or her positions during the discourse. But it does mean that comments of a personal nature are off limits. And accordingly, that comments not be taken personally by those to whom they are directed. And I will try and set an example by intervening where appropriate.

But I think it is up to everyone to hold each other responsible for maintaining a high standard of conduct during the meeting. So that is a little bit of the philosophy. Now I will talk more about the meeting and I will try and set up what we hope to accomplish in the next two days.

(Slide.)

The objective of the meeting is to consider the merits of the risk assessment. We did do a risk assessment. It should be out on the front table. We apologize in advance for the short time that it has been available to the public. It has been available the same amount of time to us.

But we want to discuss the merits of the risk assessment as a potential model for evaluating the risk to human health from resistant food-borne pathogens associated with the use of antimicrobials in food animals. The risk assessment itself is very specific. It deals with one specific aspect of resistance. And we will discuss that considerably.

But what we really want to know, the real purpose of introducing the risk assessment is to ask the question is this a good approach; is this risk assessment applicable to dealing with the entire whole issue of antimicrobial resistance; where does it fit in. So those are the kind of issues that we would really like to get your opinions on. Not so much the specifics of that particular risk assessment, but how it might fit into a greater regulatory scheme.

And then what kind of criteria should CVM consider in evaluating the risk of certain pathogens; how do we define such things as an acceptable level of risk, as harm; what do we define as harm; what do we define as the population that we are considering protecting. These are questions that will come up during the course of this discussion.

(Slide.)

We started out a little more than a year ago. It was on November 18th. And we issued a guidance document in the Federal Register. And it said that -- it basically said that emerging scientific evidence indicates the therapeutic use of antimicrobials in food animals in addition to sub-therapeutic food uses may select for resistant bacteria of concern to human health.

It also said that the FDA believes that it is necessary to consider that potential harm, human health impact of microbial effects associated with all uses of antimicrobial drugs. So that is -- that started this process.

(Slide.)

That was followed last December, almost one year ago to the day, with a framework document that most people I think are familiar with. And that framework document said that it was an attempt for FDA, as I indicated earlier, to provide its thoughts on what might be a rational approach to dealing with the issue of antimicrobial resistance from a regulatory perspective.

And it says that FDA's position is that the regulatory system for antimicrobials for use in food animals should be modified to address the issue of microbial safety. And it should look at the importance of drugs. The framework document takes a risk-based approach in that it looks at the risk as it relates to the importance of the particular antimicrobial drug or class of antimicrobial drugs for human -- the importance in human medicine.

And it also talked about such things as setting acceptable levels of risk thresholds and those kinds of things that would be important from a regulatory standpoint.

(Slide.)

A number of comments were received. And I think one of the comments that we heard time and time again was that we, the FDA, before we take any regulatory action should conduct a risk assessment to determine exactly what the harm is from exposure to the public to resistant microbes.

And so we listened to that and we contracted with an expert in risk assessment. And you will hear from him later, Dr. David Vose. And he helped develop the model that you -- that we published last week. So CVM's risk assessment was really -- it was a pilot project. We weren't sure at the time when we entered into it if we would actually be able to pull it off. But I think we have.

We learned a tremendous amount just by going through the process. And we wanted to -- the risk assessment does model the risk associated with fluoroquinolone-resistant Campylobacter originating from chickens. That is the subject of that particular risk assessment. And we want to know if that model that we propose today in some form might be used as a model for looking at the whole entire issue of antimicrobial resistance.

(Slide.)

Some people had asked, well, why did we pick this particular microorganism and drug in chickens in this case as the model. Well, there were a number of reasons why we chose this particular combination of fluoroquinolones, chickens and Campylobacter. First of all, chickens are a reservoir of Campylobacter and Campylobacter is one of the most common of the food-borne diseases and Campylobacter -- excuse me -- Campylobacter do have the ability to develop resistance quickly to fluoroquinolones.

And fluoroquinolones are often used empirically in the treatment of patients that have food-borne disease. And probably as important as all of those other contributing factors is that we actually were able to obtain data, real data that we could use to model the risk.

So for all of those reasons, that is why Campylobacter was chosen as the first one. It is probably one of the simplest of the -- of all the food-borne diseases that we can model. And so that is why we chose that one.

(Slide.)

Let's talk a little bit about the agenda for the meeting. For this morning, we will have a general description of risk assessment tools, a discussion of the epidemiology of Campylobacter, and presentation of the risk assessment, the risk assessment that we published. This afternoon, we are going to talk about the use of risk assessment by various other agencies, looking at the issue of food safety or water safety.

The second part, we will have a discussion of the epidemiology of Campylobacter -- oops, not -- we will have a panel discussion looking at risk assessment. And we will adjourn at 5:30 sharp. That is what time our transcriber has indicated that she needs to leave. So we will try and, again, adjourn at 5:30 sharp. There is going to be a small reception that will occur at some other time, somewhere between 5:30 and 6:00 as I understand.

Okay, Friday. On Friday, we will meet again in the morning. Session 2 will look at the overview of the assessment of risk by U.S. regulatory agencies. In the afternoon, we will have a panel discussion on how based on all of the things that we have heard to that point, looking at what other agencies are doing, etcetera, how should CVM evaluate the risks; how should CVM look at antimicrobial resistance within the context of the other regulatory agencies.

And we are going to on both days seek public comments. We want a lot of public comments. Finally, we will end the session by talking a little bit about what the next steps are about how we might go about with the process of setting regulatory thresholds for resistance.

(Slide.)

Okay. In addition, because we are not going to be able to get everything decided here at this meeting, we think this meeting will provide a lot of food for thought and the people will want to go back home and reflect on what has occurred, read the risk assessment a little bit more carefully, look at the Framework Document, all of these things, and then provide comments on their own personal thoughts about what should be done.

And the comments can be sent to this docket. And we will provide a full transcript of this meeting. It will probably be put up on our home page sometime following the meeting so that everybody has the opportunity to determine -- to know what actually transpired at this meeting. We really do need a lot of public input on this.

(Slide.)

Before I turn the podium over to Dr. Beaulieu to introduce the first panel, I would like to take this opportunity to recognize some of the people in CVM who went way, way beyond the call of duty to bring us to this point where we could hold this meeting.

First and foremost, I would like to recognize Dr. Sharon Thompson, Associate Director for Veterinary Medical and International Affairs at the Center for Veterinary Medicine. Sharon is one of those exceptionally rare individuals that I can charge with an impossible assignment and know with complete confidence that she will accomplish it on time, under budget, and exceeding all expectations.

I would also like to recognize Kathy Hollinger. Kathy is a veterinarian and an epidemiologist par excellence. During the course of developing the risk assessment, we were told repeatedly by the experts that what we were trying to do was impossible because the data needed to support the model simply didn't exist. And Kathy proved all the experts wrong.

Through self-motivation and shear tenacity, she was able to obtain data that were thought to be unobtainable. And I believe the term that we use for that today is data-mining. And she is the best miner that we've got. So I want to recognize her.

Mary Bartholomew -- I put "Dr." up there, but it is pretty close to the truth now. Mary is our statistician who expended a great deal of effort in assisting our risk assessment consultant, David Vose, to develop the mathematical and statistical elements of the model. So we really want to recognize her.

Marsha Larkins is CVM's ombudsman. But in addition to her regulatory duties, she was responsible for coordinating CVM's response to the enumerable comments on the Framework Document. And, again, that should be available out on the table.

Alita Sindelar is the newest member of the CVM team. She assumed the responsibility for planning three public meetings on antimicrobial resistance including the one that you are attending here today. And this is how it worked, this is how the CVM management works. CVM management decided that to get to the point that we are today, we needed to respond to all the comments from the -- on the Framework Document, develop a risk assessment, and then through some miracle hold a public meeting before the millennium.

Marsha Larkins got the framework comments assignment. Sharon, Kathy and Mary got the risk assessment assignment. And Alita got the miracle assignment. And she has performed outstandingly.

Finally, I would like to recognize Ms. Linda Kawatch for her help in putting this meeting together. All the myriad of minute details that go into putting a meeting like this together are something that most of us never consider, but are so terribly important. And what Linda has done in the past few weeks alone is the kind of work that is usually done by whole staffs and other organizations. So we really wanted to make sure and recognize those people.

(Slide.)

I want to recognize a number of organizations that contributed to this. And we absolutely could not be where we are had we not had a tremendous amount of assistance from these various organizations: Centers for Disease Control and Preventions, especially the National Center for Infectious Diseases is a critical partner in our being able to not only obtain a lot of the data that went into the risk assessment, but also NARMS could not exist, absolutely could not exist without CDC's input. So an absolutely critical player.

A similar critical player is USDA's Agricultural Research Service who are -- whose laboratory is helping us in actually doing the antimicrobial resistance monitoring for the animal specimen. NARMS couldn't exist without ARS either.

Food Safety Inspection Service of the USDA has been wonderful in providing us with access to the animal isolates from the HACCP programs from the slaughter houses so that we can conduct the NARMS system. Economic Research Service, the Census Bureau, the National Chicken Council and the University of Pennsylvania all provided valuable information that went into the risk assessment.

(Slide.)

And finally, I would like to recognize the American Veterinary Medical Association for -- under the heading of risk management for their outstanding commitment to develop and promote judicious use of therapeutic antimicrobial drugs in veterinary medicine. They have supported it with their dollars. They have supported it with their resources and efforts and convening people. And I didn't want to get -- let the opportunity get away to express how important CVM thinks that committee is.

And with that, I am going to turn the meeting over to the Deputy Center Director for Veterinary Medicine, Dr. Andy Beaulieu.

INTRODUCTIONS

Dr. Andrew Beaulieu

DR. BEAULIEU: Thank you. Steve. Good morning, all. I am Dr. Andrew Beaulieu, recently appointed Deputy Director of the Center for Veterinary Medicine. I want all of you to know that up until July 19th of this year, all of this hair used to be brown. And a large part of the reason for the change is the issue we are here to discuss at this workshop.

In fact, this change may be one more potential effect of antimicrobial resistance that we may want to investigate in the future. Actually, it is not true about the hair, but it feels like it should be.

This is -- I have to say that this is the most complex scientific and regulatory issue that I have encountered in my 27 years in CVM. There are no simple solutions to this problem. It will take all of us working together to devise a regulatory system that appropriately protects both human and animal health.

As part of that process, I welcome you all to what I hope will be a very constructive discussion of what may become an important component of such a regulatory system, quantitative risk assessment. And on that note, I have the pleasant task of introducing our speakers this morning starting with Dr. Wes Long.

Wes Long began his government career in 1991 in the Center for Food Safety and Applied Nutrition's Office of Pre-market Approval. Wes' current position is at the FDA --

is as the FDA Associate Scientific Director for the Joint Institute for Food Safety and Applied Nutrition, typically known as JIFSAN, with primary responsibilities for coordinating the development of collaborative programs between the University of Maryland and the FDA in the area of risk analysis.

In addition, he chairs the Interagency Risk Assessment Consortium composed of 18 federal agencies with food safety risk analysis responsibilities. And Dr. Long will speak to us this morning regarding the question what is risk assessment, risk management and risk communication. Wes.

As Wes is making his way up, I would ask our speakers -- Wes and the rest of our speakers to try to allow a couple of minutes for questions at the end of their presentation. I will facilitate that process by allowing a couple of minutes on the timer for that purpose.

WHAT IS RISK ASSESSMENT, RISK MANAGEMENT AND RISK COMMUNICATION

Wes Long, Ph.D.

DR. LONG: I want to thank the Center for Veterinary Medicine, Steve and Andy and Sharon for inviting me to give you a little bit of a primer on risk assessment, risk management and risk communication. I think it is to CVM's credit that they thought it was worth their time in a very busy agenda for today to allow a little bit of time to make sure we all have a common basis and understanding for this area of risk assessment and how it fits into risk analysis.

(Slide.)

I think that -- well, I know that there is potential for a great deal of confusion when you start to talk about risk assessment. I spent the last three days at the Society for Risk Analysis Annual Conference in Atlanta. And these are 2,500 risk analysis professionals. And even they can't agree on what is the difference between risk assessment and risk management. So you are not alone if you have trouble with this, these different concepts and sorting them out.

You are going to have a lot of information coming at you over the next two days, a lot of science, a lot of sort of hard core science. You are going to have some risk assessment modeling that you may find difficult to understand. There will be discussions of legal statute. There will be opinions. There will be discussions of standards.

And I think it is important that as CVM is actually here to learn what you think, that it is useful to provide you with the tools to effectively communicate with CVM your opinions and your needs and your perspectives.

(Slide.)

So we are going to start off with a little test. I hope everybody got a good night sleep. No, not really. If we just look at the title of the meeting, Workshop on Risk Assessment and Establishment of Thresholds, actually right here in the title, some of you may know and maybe most of you know that actually risk assessment is risk assessment. Establishment of thresholds is risk management.

So already -- now, risk assessment, of course, is a tool for the risk management aspect of establishing thresholds.

(Slide.)

Let me explain. First of all, I will show this slide. And if a Power Point slide could get tattered, this would be my tattered slide. Risk analysis actually is composed of three components that are interrelated: risk management, risk communication and risk assessment.

(Slide.)

All right. Well, what is risk assessment? One way to describe what risk assessment is is that it is a tool to predict the likelihood of the occurrence of an adverse event.

(Slide.)

Now, if this is a little bit too complicated and we want to back up a step, then we can think of risk assessment as looking at what can go wrong, how likely hazard is likely to occur and what are the consequences if it does happen.

(Slide.)

Again, while risk assessment is a tool to predict the occurrence -- the likelihood of occurrence of an adverse event, it is also a science-based technique for organizing our information and separating what we know from what we don't know, and then taking this information and presenting it to our risk managers as well as to fellow risk assessors and fellow scientists for their critique and analysis.

So this presentation of relevant scientific facts needs to be structured to clearly tell what we know, what are the data sources we used, what information did we rely on. It needs to characterize how well we know what we say i it is that we are knowing. And it needs to be transparent to reveal any biases that the risk assessor might have and also to really pull out the simplifying assumptions because it is often necessary with data gaps to make simplifications and assumptions that may affect the analysis.

(Slide.)

All right. Well, but that is not enough. Risk assessment really has to try its darnedest to answer the question. Whose question? It is the risk manager's question. And without a good communication between the risk assessor and the risk manager, then the risk assessment can end up coming up with something that really does not address the needs of the risk manager to make the decision that the risk manager needs to make. What happened here?

(Slide.)

Okay. So what are the questions that this risk assessment is trying to answer, like Dr. Sundlof said? What is the extent of the risk to human health from resistant food-borne pathogens associated with the use of antimicrobials in food-producing animals? That was the question put to the risk assessors.

(Slide.)

What questions does this risk assessment not answer or not attempt to answer? It is not going to tell you what the level of risk that expresses a quantitative definition of acceptable risk is.

(Slide.)

And if that is too much gobblety-goop, it is not going to tell you what the appropriate level of public health protection is.

(Slide.)

The risk manager -- those are all considerations for risk management. And there are a number of considerations that risk managers have to consider when they go to make a decision. And certainly the science is critical as Dr. Sundlof noted. FDA is a science-based organization and we try our darnedest to base our decisions on the science.

(Slide.)

But there are other factors, as well. There are public values. There is an expectation from the public about the safety of the food supply and the degree of protection that is necessary. And there is a relationship between those expectations and the perceptions of the public of where we stand at this point in assuring that sort of safety. Public values also include stakeholders from producers, farmers, manufacturers, as well.

(Slide.)

There are economic factors that have to be considered. And if there is a result in rule-making down the road, that rule-making will include an economic assessment that will look at the costs and benefits of any alternatives, as well as looking at the competing benefits of different technologies and the cost of those technologies, as well.

(Slide.)

Statute, I think you will hear more today about how statute describes FDA's authority to act, but it also places some limitations on what those actions can be that FDA can take.

(Slide.)

And finally, there are always going to be political factors. And here when I say political factors, I am not talking about Congress putting the thumb screws on Dr. Sundlof based on his decision. But rather about the political priorities and how this fits into the broader range of concerns of the Center and the Agency and the needs of the Congress and White House.

(Slide.)

Okay. Briefly I am going to mention risk communication. I have already mentioned the risk communication between risk managers and risk assessors. This is in framing the question and monitoring. While you try to maintain a functional separation between the risk assessors and the risk managers, they have to communicate with each other.

(Slide.)

There is communication between the risk assessors and the scientific community. And I hope that we are going to hear some of that communication today as this greater scientific community evaluates the risk assessors' use of the available science.

(Slide.)

There is communication between the risk managers and the stakeholders. And all of you here today are stakeholders in one way or another.

(Slide.)

And finally, and sort of in a separate category is the risk managers communicating their decision, the final outcome of this meeting and the rest of the meetings when FDA does get to the rule-making stage. How do we get the message out?

(Slide.)

Okay. So to summarize, risk analysis is composed of three components: risk assessment, risk management and risk communication. Risk assessment is the technical work. Risk management is the decision-making. And risk communication is the way we get risk management and risk assessment to work together in conjunction with stakeholders.

(Slide.)

Okay. So what is CVM hoping to get from this workshop? I think in terms of your input today, we are spending most of our time critiquing the assessment, understanding risk assessment principals. And so the questions are is the risk assessment understandable, does it have utility, is it a fair presentation of the available data and information.

And speaking as a risk assessor, risk assessors always want to make their risk assessments better. And one of the best ways that they can make those assessments better is to have more and better data. So certainly if you are knowledgeable about data that is available that wasn't utilized that perhaps should be utilized, I am sure the risk assessors in the audience would be thrilled to have that information.

(Slide.)

Okay. So today -- I say tomorrow on the slide. But today and tomorrow, the risk managers are going to be listening. They want to know what you think about the risk assessment. As they evaluate the assessment, they want to know your evaluation of the assessment, as well, to incorporate it into their decision-making process.

And they are also going to be looking for your opinions on risk standards and the role on how this risk assessment fits into developing and setting those standards and thresholds. So I hope you all can use this information a little bit to help direct your questions and your comments today. Thank you.

DR. BEAULIEU: Any questions for Wes?

(Applause.)

DR. BEAULIEU: Sorry. My question was premature. Any questions for Wes? Thank you, Dr. Long. Our next speaker this morning will be Dr. Lester Crawford. Les has a D.V.M. and a Ph.D. from some places down south. He is currently the Director of the Center for Food and Nutrition Policy at Georgetown University.

In former lives, he was an administrator of FSIS/USDA and an Executive Vice President of the National Food Processors Association. And he was an Associate Dean at the University of Georgia and also something I am having -- oh, yes, he was former Director of the Center for Veterinary Medicine.

(Laughter.)

Les is going to talk to us this morning about the use of risk assessment in regulatory decision-making.

USE OF RISK ASSESSMENT IN REGULATORY DECISION-MAKING

Les Crawford, D.V.M., Ph.D.

DR. CRAWFORD: Thank you very much. Congratulations to Steve and to Andy on the risk assessment and also on this meeting and thanks for asking me. I, among all of you here, probably are the only one that remembers when your hair did turn white, Dr. Beaulieu.

(Laughter.)

And it was one of the most astonishing moments of my life. I was sitting there being grilled by the Honorable Ted Weiss. And I was trying not to look at him because that was an unspeakable thing to have to do. So I was turning my head away. And I could see the friendly face of old Andy Beaulieu in stark terror.

(Laughter.)

And then Weiss invoked the name of Andy Beaulieu. And I turned and looked at Andy. And all of a sudden, his hair had gone from deep brown-black to white in one fell moment.

(Laughter.)

Risk assessment, the use of risk assessment in regulatory decision-making is what I am charged to discuss this morning. And I would like to begin by talking a little bit about the transition between toxicological risk assessment and microbial risk assessment and then finish by the recent adaptation by U.S. Government and also WHO to microbial risk assessment as a tool in the evaluation of antibiotic resistance and how that fits into the regulatory climate and calculus worldwide.

The first real use that we made when I was in the government of risk assessment happened in a curious way because we had showed the courage to ban DES, diethylstilbestrol, in the year 1979 when I was Senate Director. And if you think this will turn your hair white, Steve, you should have seen those days.

We were not -- we had the courage to ban it. But the cattlemen of the United States did not have the courage to stop using it. So we faced a Constitutional crisis. And one fine day, FDA/CVM had to take possession of 500,000 steer throughout the United States.

And we had people like the Under Secretary for Food Safety at USDA calling for their euthanasia. And the only way we got out of that was to do a risk assessment which showed that the cattle could be held for 63 days, their ears surgically excised or amputated depending on the situation. And we had that done to half a million head. And it was based on a risk assessment. And I suppose that is probably the first time I had ever heard of risk assessment.

And then following that, the risk assessor, who was Joe Rodericks, now is one of the principals in Environ, contracted with the National Academy of Sciences to do a series of three meetings similar to this and similar to what WHO did to develop toxicological risk assessment using the DES risk assessment as a model.

Some of you, like me, may have attended and participated in those meetings. But when we came out of there, we had both routinized risk assessment and we also had made it available as a regulatory tool and as a legal tool which we needed the latter most desperately at that time.

It remained for us to decide what the level of risk was. And so the Commissioner of FDA, Dr. Hayes at the time, ordered what he considered the four risk managers in the area locked up at the Xerox Center in Leesburg, Virginia to decide on a level of risk for a number of exercises and for FDA in general.

Those were Mark Novich who was Associate Commissioner for Medicine -- Medical Affairs, Sandy Miller, me and Tom Scarlett who was the General Counsel. And the issue was to decide whether or not we would have one in 100,000 risks, one in a million or one in a billion. And it was not possible given our dim understanding of risk assessment to decide which was best. And, of course, we were prone to use the political route.

And about 11:00 p.m. on the last night that we were to be freed the next day to go back to our jobs, we all had a different figure except for Tom Scarlett who as a lawyer was wise enough not to give his opinion. But he was finally forced into it and he did it in a way that I shall never forget. And I suppose this is the reason we have the risk assessment and risk figure that we have.

He said, "Well, I haven't said anything now in about six hours. So it is time for me to say something." And he said, "I was just sitting here thinking. We are still struggling between one in a million, one in a billion and one in 100,000." He said, "I think one in a billion is just out of the question." And he said, "I have never heard, I don't think it would be popular to use one in

100,000 because thinking about it, I have never heard a young man say to his sweetheart, 'My darling, you are one in 100,000." So we voted then for one in a million. And we went home.

(Laughter.)

Following those exercises, the next thing that happened of note was the World Health Organization under the leadership of Fritz Kafferstein who has now become something of an American put on a series of four meetings starting in 1995 and finishing in last spring, 1999, to define risk assessment for microbial concerns.

And these four reports, including the last one, are now available. And some of the same people who were out at Leesburg chaired those meetings. And I think they will be used now throughout the world, certainly in the countries that belong to the World Health Organization which is virtually all.

And many countries, particularly in this last one that I was involved in, made major investments in time and in funding in order to make sure that they had this tool done by this international organization. So the time of risk assessment as a regulatory tool is certain here.

Now, I like risk assessment. And I think that I would live a lot longer had I had it and had it been routinized and been the subject of some rigger when I first started out in my regulatory career. I think it takes the politics out of food safety to some extent. And I will give you some examples of that.

You recall in the European Union-U.S. dispute over hormones, when this came before the World Trade Organization three years ago and the ruling came down, the EU pleaded not to have to yield to the finding of the WTO which, of course, found in favor of the United States and specifically in favor of FDA/CVM. The EU appealed not to have to do that until they could do a risk assessment.

And they assumed it would take 15 months to the day to do the risk assessment. And they proceeded then to hire some risk assessors for the first time, and also were painfully at a loss to explain the fact that they had never done a risk assessment before on this subject which meant that they didn't know whether they were safe or not safe because they had never thought about it.

But the power of that as a political and regulatory and public health tool was I think forever enshrined in the world as a result of that. If a risk assessment was so important to the decision process in something that is probably one of the major regulatory disputes of all time historically, if that was the case, then we have risk assessment as a tool that is enshrined then forever.

And then a little later, they decided to evaluate feed-additive antibiotics. And in the pressure of the moment in having forgotten their commitment to risk assessment, they took action against several antibiotics without benefit of clergy or of a risk assessment.

I think probably they will now have to go back at some point in history and do that. So the lesson to me is clear. And also, the concept of the risk manager.

I have been involved since the WHO meeting last spring in a number of seminars and meeting with various governments -- we are doing this with Brazil next month -- and trying to the ministers -- never have I met one that was qualified in regulatory affairs or in medicine or science -- explain to them that the role of risk manager is what they really are and what is a risk manager and how do you react and what is risk assessment, and isn't it great that you are the risk manager for this country and you are going to have more fun with less trauma than you ever thought you would because of that.

And it is working. It is working around the world. And it links in a fundamentally important way and mathematically even the risk assessors with the risk managers. And the public is all the enriched buy because it is a transparent affair. It is not something that sneaks up on them.

And it really is what the world is demanding, for example, in the battle in Seattle on biotechnology. That is really what they want. And I am not sure they would be willing to live up to the outcome. But that is what they want.

And the other thing I would say is that risk assessment is becoming the international language of food safety. Food safety, you are either going to have a risk assessment mentality and a risk assessment that is enshrined in government or you are going to have a situation where you have a learned oligarchy making decisions for the people.

And I have been somewhat part of that and I thought it was great. But the public doesn't think that's too great. And the first time I ever heard how hateful it was was when we were trying to sell the general agreement on tariffs and trades in the sanitary and phyto-sanitary amendments to that.

I appeared around a lot of different places telling them how great this was going to be. And I had that unhappy assignment. And what people would say, "Well, what CODACS really is a bunch of little gnomes meeting in Rome and in Geneva every two years. And they decide all these horrible things for the world. We don't want any more of that. It is not transparent."

And up until that time, I had always thought transparent applied to a window pane. But I knew then what it meant and I knew that risk assessment was probably the way we would get out of that. And we actually wound up having to pledge to go in that direction.

In the United States, as all of you know, there is pending in Congress a bill called the Regulatory Improvement Act of 1999 which would make risk assessment law and would require it for all regulations that have to do with public health and virtually any other thing. Whether or not the bill passes this year is academic.

It was introduced last year. I think it will continue. And I think it will eventually pass. And it would require the Office of Management and Budget not to lick their fore finger and hold it up to the wind, but to actually evaluate what these regulations are going to do for the public, or do to them. And I think that is great.

And then the next thing is we had a meeting at Georgetown last month. And the World Trade Organization representative talked about the fact that they are now incorporating the requirement for risk assessment in all of the issues and disputes that they take on. And that is now a matter of legality with them.

And he modeled -- he said he modeled their amendments after the Regulatory Improvement Act of 1999. So it is passed worldwide and it is still pending in the U.S.

like some other things have throughout history.

So -- and then, of course, CODACS has further more enshrined it. The EU has. And I think we are seeing history being made. And I would mention several models that I think are -- in closing, Dr. Beaulieu -- that I think are going to define this for us.

The Georgetown model that Steve Anderson will present a little later on we had a great deal of fun with. And we also learned. Some of the lessons we learned were difficult. But we are now ready to do them and we are starting another one which Steve will also mention.

The FDA model which I got the same time all the rest of you did certainly plows new ground. It is a document of historical significance. The model in Canada by Anna Lamberding. There was work done in the United States by Bob Buchanon and others which we will hear some more about today.

It is just actually like a textbook to me. I think if you want to learn about how you use it in regulatory decision-making, you need to get that first and foremost. And then the Listeria monocytogenes, which is being broadly trashed around the world even as we speak, but nonetheless will be a good risk assessment model and I think will probably plow even better and newer ground than the SE model did.

So we now have -- we have had the philosophy. We developed the science thanks to WHO. And now we have what is needed in order to make this a discipline and a very strong discipline in regulatory decision-making. And that is some actual models to look at, teach from and learn from.

So with that, Dr. Beaulieu, I will conclude my remarks. Thank you.

(Applause.)

DR. BEAULIEU: Maybe time for one quick question for Les if there is one. Okay. Thank you, Les. Our next speaker is Dr. Doug Powell. Dr. Powell has a Ph.D. in food science from the University of Guelph. He is currently an Assistant Professor in the Department of Plant Agriculture at that university.

He is co-author of a text -- or maybe not a text, but a book on Mad Cows and Mother's Milk which is a series of case studies involving risk assessment, management and risk communication. And he is here today to talk to us about the importance of risk communication in the development of science-based regulatory requirements. Dr. Powell.

THE IMPORTANCE OF RISK COMMUNICATION IN THE DEVELOPMENT OF SCIENCE-BASED REGULATORY REQUIREMENTS

Doug Powell, Ph.D.

DR. POWELL: Always fun going after Lester. AV person? There we go. It keeps moving. There we go. Okay. I am going to make my comments brief and talk about the role of risk communication. You are going to hear a lot about risk assessment over the next two days. And Lester certainly gave a good overview.

I want you to keep in mind though the risk assessment works best when your expectations are not too high. And the reason why is other industries have gone through this where if we can just get the science better, we will have a resolution to these difficult public policy questions. And they are disappointed.

(Slide.)

This is the model. I know FDA uses this in some of their other regulatory areas. It is from a 1997 Presidential Commission on Risk Management. And basically what it says is -- you know, in the past, it was assessment and then management and then communication, a very linear separation.

This is more than just circles. It is not just because it is the '90s and we are all holistic and draw circles. It actually is a very powerful model that says to integrate all three of those things. And what it really says is you need really good science, but you also need really good communications. And the reason why is because there is so much uncertainty in a risk assessment that you can't just rely on the numbers.

(Slide.)

For consumers, they often view these things as stigma or stigmata. And the risk assessment isn't actually that important. Consumers might not know all the details of bovine spongeiform encephalopathy and new variant Creutzfeld-Jacob disease. But if I say British beef, there is generally a yuck factor. That is a stigmata. That is a short-cut that consumers use.

And for a regulatory agency, they have to be aware of that and keep that in mind. And the characteristics apply quite nicely to the use of antimicrobials in animal agriculture. There is a hazard. There is a potential for risk, a standard of what is right and natural. You know, why are we doing this is somehow violated or overturned. Impacts are perceived inequitably. Lots of scientific uncertainty. This is normal for any risk scenario.

The bottom line is the management and the hazard is brought into question. And that is critically important and that is why you have meetings like this, is so that you have a clear and transparent management of hazard.

For example, think of the dioxin in Belgium crisis that happened earlier this year. We just reviewed about 300 stories. I mean, it gripped Europe for a couple of weeks. People were talking about, "Oh, my God, we can't even get food on the table." Grocery stores were empty.

And out of those 300 stories, we found one, one that talked about the actual risk to human health and safety in terms of consuming the stuff. The other 299 were all about how the hazard was managed and the fact that the Belgium government knew for six weeks and didn't bother telling anybody and directly led to their electoral defeat.

So management of the hazard is critical in terms of -- because what happens is something is stigmatized. Things go off the rails. And it is very difficult to have a meaningful discussion using all the great science of risk assessment.

(Slide.)

So we need good surveillance systems. And I would argue that you generally have that. They can be improved. Good communication. A credible, open and responsive regulatory system. That varies from agency. It varies by country. Demonstrable efforts to reduce levels of uncertainty in risk and evidence that actions match words.

(Slide.)

Surveillance, I am not going to go through this. You basically have a good system through FoodNet, PulseNet and NARMS. You are getting some of that basic data which can feed into the risk assessment that needs to be improved.

(Slide.)

Risk communication has been around for at least ten years if not more. This is the long definition from the National Research Council. The short definition is any conversation about risk which is usually with your spouse.

(Slide.)

This is the history of risk communication. And there are some powerful lessons in here as you embark on risk assessment for antimicrobials. Baruch Fishoff pulled this together a few years ago. In the early days, it was thought all we have to do is get the numbers right, make the risk assessment better. We will get better numbers. We will have answers. The nuclear industry went through this.

It doesn't work that way. It's like you are one in 100,000. People only remember the one. All we have to do is tell them the numbers. You know, if we educate the public, then clearly we will be able to understand this better and we will resolve conflict. Say what we mean by the numbers. This is risk analogies, you know.

These numbers, one in a billion or one in a million. People can't get their minds about it. So we have to use analogies like, you know, well, it is like a marble in a beach full of marbles the size of the United States or, you know, analogies like that. And that tends just to make people mad because what you are doing is trivializing concern.

Show them they have accepted similar risks in the past. Well, you know, you drove here so what are you worried about this for? How many times have you heard that one? You know, these guys have figured it out to get rid of this about 15 years ago. But we still hear it all the time.

Show them that is a good deal. Can you buy people off? Actually, you can sometimes in citing hazardous waste facilities. They always promise, you know, a lot of jobs and there is usually one part-time that ends up getting employed.

Then we went into -- in the early '90s, we went into what I call the happy talk phase of risk communication. And that is if we just treat people nice, we can get rid of conflict and come to some solution. We make them partners. And, you know, Clinton was certainly a man of the time. Remember, when he was elected originally in '92, he was the empathetic President. He was apparently a little too empathetic. He felt a little too much pain.

(Laughter.)

And now we've gone past that. Canadians export Canadians and hockey players. I am trying to uphold that standard.

(Laughter.)

And the bottom line is all of the above, we need all of that. It is not enough just to talk nice to people.

You've got to have the data to make it meaningful.

(Slide.)

Now, with antimicrobials, this is generally the state of public discussion. You get stories like this. I am not going to go into it.

(Slide.)

The New York Times, oh, look, fluoroquinones and chicken. That was last -- two years ago.

(Slide.)

Certainly, there has been a dramatic increase in media coverage over the last couple of years of antimicrobials, in particular, the agricultural use of antimicrobials leading of course to a huge increase in antibacterial products out there, both for microbial food safety concerns and other concerns which do nothing but accelerate development of antimicrobial resistance. However, they are all out there.

(Slide.)

FDA has entered into the fray. It has gotten a lot of public coverage since last January on a proposal to manage antimicrobial resistance. And I think there is good recognition that these things are not direct anymore, that there are environmental impacts and that really we aren't talking about the environment.

It is not just a matter of plants are over here and animals are over here and humans are here. There is -- while there are different arenas, there certainly is a lot of cross-fertilization. And I mean that literally with manure.

(Slide.)

One of the solutions then in the absence, while the risk assessments are going on, while you are improving your science, it is important also to demonstrate the management of that risk. And we have judicious use principles or prudent use guidelines. I think the Americans are on the judicious use. And a lot of the species have these things.

But what is important then is, you know, it is not just a matter of talking nice to people. You have to have data where people are actually doing it, evidence that actions match words. So in order to do that, I am going to talk about tomatoes.

And you may be wondering what's that got to do with it. Well, actually a lot of antibiotics are used on field tomatoes to control bacterial diseases. And this is another one of the environmental loads. And I think there is a growing recognition of that.

(Slide.)

When you work with producer groups in order to implement these things, and we do this sort of stuff, we always find it useful to go out and survey them. You know, people always talk about surveying consumers to get their perceptions. We are also interested in perceptions of producers because if they are actually going to implement something to reduce and manage risk, they've got to own it.

And we've done this three times now with three different groups. And we asked people the same question we ask consumers which is an unprompted what is the greatest threat in the food supply today. And the producers always say imports. And it doesn't matter what country we ask, they all say imports.

And this is expected from a risk perception viewpoint because individuals are impervious to risk. In the United States, you know, there are surveys done every year: Is drugs a big problem for society? Absolutely. Is drugs a problem in your family? Uh-uh. Well, where is it all coming from then? Well, it is out there. It is someone else. So you need a mind-set change to demonstrate that it is their problem and they have to own it.

(Slide.)

And this is a greenhouse tomato facility which is not important. What is important is this sort of stuff. You can develop judicious use guidelines and produce manuals. And we all have the QA programs which feed into those. But manuals aren't enough because you don't have any evidence anyone has actually read it, let alone done anything about it.

(Slide.)

As this cartoon says, it has, "Our annual ISO 9000 audit is next week. We can pass the audit if we put all of our nonconforming documents in the trunks of our cars and then torch the cars." Doesn't that defeat the purpose of a voluntary audit?

(Slide.)

But one of the things we did with this particular producer group that I think is instructive for implementing prudent use guidelines and communicating with producers and others who have responsibility to manage this risk is we can document changes. For instance, when we ask them, "What are the greatest threats to the food you eat?", in 1998, after imports it was pesticides. By 1999, just after a couple of rounds of meeting and after throwing the manual out, storage and handling and microorganisms were all of a sudden on the list.

(Slide.)

More importantly, we asked them about particular programs they had implemented. And this is for microbial hazards. And in '98, they had barely heard of it. They were talking about reduce pesticides and biological control.

By one year later, we are all of a sudden able to show that the number one thing is they have improved their cleanliness. They are starting to think about keeping the place clean. What a concept. But for fresh produce, this is something that is relatively new.

Hand washing and washroom facilities, not even on the list in '98, are suddenly coming in quite high. So we are able to demonstrate that there is at least an awareness. But, you know, people can lie on surveys.

(Slide.)

So you go an additional step. And that is we have a student actually collecting data full-time on end product and on water quality and doing pathogen testing. And that is the data which supports the claims that they are making.

(Slide.)

So as you move forward on implementing, whether it is judicious use principles for initial management because Lester and his group can be doing risk assessments for the next 20 years and they will always be getting better. That is not to slag risk assessments. The alternative I think is astrology. And what Lester said is correct.

But don't put it up on a pedestal because it will get knocked down. It is a useful tool to provide incremental, yet significant improvements in understanding. There are a lot of data gaps at this point that need to be filled to improve that understanding. But we can't wait because you can be -- you can always do a better risk assessment. And that is the point.

In the meantime, you have to demonstrate that you are aware of the risk and are taking actions to reduce risk. And while you are doing that, you need good risk communication. And what we have shown is that, you know, you have a scientific perception of risk. You have a public perception of risk.

And I am not going to go through that today. But in between is the activity of good risk communication, entering into public discussions about levels of risk. And there is a very high level of awareness on this issue from both the medical side and an agricultural side.

(Slide.)

So as you enter into that, just some general lessons that we have learned from previous case studies and some even involving the Center for Veterinary Medicine around BST for example. A risk communication vacuum if allowed to develop is why things end up on the front page. It is exactly what happened in Europe over genetically engineered foods which is another fun topic.

Regulators and industry and academics and producers, everyone is responsible to communicate effectively about risk. And if you are responsible, do it early and often because you won't like the results if you wait. There is always more to a risk issue than what science says. And I think we are going to spend the rest of the meeting talking about what science says.

But just keep in the back of your mind that when you leave here, there will always be something additional that is not necessarily about science. Even though FDA does not have a legal mandate to assess that and that's proper, just in terms of communication, you have to be aware of that.

Educating the public is generally a non-starter. Most people do not want to be educated or they would all be here. Most people want to go shopping, not do homework. They want to go to their grocery store and have a level of confidence so that they can focus on handling the screaming kids, not whether this thing has some sort of problem.

And it is incumbent on the regulatory agencies to generate that level of trust and credibility, that level of confidence in consumers.

I think everyone has agreed that the no risk thing is out the door. You don't hear it very often, at least not in the United States. Risk messages should directly address the contest of opinion. And that is because there are issues that aren't to do with science, yet they are what is going to be out there. For example, Belgium, dioxin. What was it about? The management of the hazard.

We have to address those issues and communicating well because you want to say it is safe has good spin-off benefits for risk management because it may mean you have to change what you do.

(Slide.)

Finally, to use a hockey analogy since we talked about hockey, since we export all our great players here including Wayne Gretzky -- these are my four girls. I had to -- I came in late last night because I coach hockey and had to stay for that because, you know, you've got to have priorities, although Scott and I missed our regular hockey game which to Canadians is somewhat tragic. And I am not sure if I've recovered yet.

You know, the NHL is really upset because Wayne Gretzky quit. You know Wayne Gretzky, right, you Americans? I've just got to check.

(Laughter.)

I know we exported him, but, you know, maybe -- the point is Gretzky was a great player, but he also was a great communicator. Now, if you watch him -- I grew up with him. He lives around the corner, or his parents do in Branford. And if you look at him on TV, he looks pretty goofy. I mean, he is about as unsmooth as it gets, scrawny and he is not too good looking and, you know, I'm not either. Maybe it is a Branford water thing. I don't know.

But the point is he went out of his way to talk to the folks who paid the bills. And that was the fans. The guy never turned down an interview even though he looked goofy. And the reason why people believed him and listened to him is when you score 1,000 goals, that is pretty good data. So get your good data and then go out and talk about it. Thank you.

(Applause.)

DR. BEAULIEU: There may be time for one quick question if there is one?

DR. POWELL: I thought we were all going to be quiet.

(Away from microphone.)

MS. : Well, this is just a general comment. Perhaps there is some insight in the room for us it would help if the ---.

DR. POWELL: Sorry. I wish you had told me earlier. You have to get out and communicate about these things.

(Laughter.)

(Away from microphone.)

MS. : Well, it will be ---.

DR. BEAULIEU: Thank you, Doug. Our next speaker will be Dr. Al Sheldon. Dr. Sheldon has advance degrees in microbiology and genetics. He is a team leader in microbiology in the Office of Drug Evaluation IV in our Center for Drug Evaluation and Research.

He has had 27 years in drug regulatory affairs, experience in drug regulatory affairs including clinical microbiology, quality control associated with drug manufacture, manufacturing and control of both bulk and finished dosage forms.

And let's see if we can't reorganize ourselves a little. I am not quite sure what cords I am running over here. Nothing seems to have unplugged itself yet. Does that help some? Okay.

I think I failed to mention that Dr. Sheldon is going to be talking to us this morning about antibiotic breakpoints, methods for determining those and their use in the medical community.

ANTIBIOTIC BREAKPOINTS: METHODS FOR DETERMINING AND USE BY MEDICAL COMMUNITY

Dr. Al Sheldon

DR. SHELDON: I will tell you that I have an autograph of Wayne Gretzky, great guy, and it is for sale.

(Laughter.)

There we go. Good morning, ladies and gentlemen, distinguished guests, colleagues from the Center for Veterinary Medicine. It is clearly a pleasure to be here today to discuss with you the establishment of interpretative criteria, i.e. breakpoints for use in human medicine.

(Slide.)

Now, before I do, I would like to discuss the regulatory process that is involved in setting up the breakpoints. The establishment of breakpoints really is a multi-step process that occurs in two different stages.

The first of these occurs during the investigational new drug stage which is the stage where the company is investigating the utility, the potential clinical utility of the drug in clinical settings. Therefore, the Agency requires that the company submit experimental preclinical data to help establish the provisional breakpoints that are going to be used in Phase 2 and Phase 3 clinical trials.

As my presentation proceeds, I will go into greater detail about the specifics regarding the requirements that need to be submitted during the investigational new drug stage.

Now, the second stage is really once the sponsor has completed all of the investigational data and they have done the analysis and they feel that the produce now can be submitted to the Agency for evaluation and approval. This is done through the new drug application stage.

In this particular instance, the Agency requires the submission of clinical data to allow evaluation of the correlation of the provisional breakpoints with the clinical outcomes that have been derived during the clinical trials.

(Slide.)

Now, this is -- this slide provides information that is very important. And it is important because it describes the methods that are used and what is required of these methods in doing these kinds of studies. We have to have confidence in the data generated during produce development. That is, it is essential that the susceptibility test method be standardized, reproducible in order to assure precise and accurate results that have been derived during the clinical trials.

It is important in doing any surveillance studies that you have accurate and reproducible methods in order to have confidence in the data that you are evaluating. Therefore, the FDA requires the use of susceptibility test methods established by standard-setting organizations. We use the methods that are established by the National Committee for Clinical Laboratory Standards.

We also determine whether a correlation exists between the MIC and dish diffusion methods that are used by sponsors. We need to understand that if an organism is considered susceptible by an MIC method, it is also considered susceptible by a dish diffusion method, i.e. for resistance.

We also establish quality control ranges. At this point, I would like to describe the fact that not only -- the FDA sets breakpoints. These breakpoints, the quality controls and a listing of this information is included in the package insert that is approved with every NDA. There is also an independent organization, the National Committee for Clinical Laboratory Standards, that also establishes breakpoints.

So we want to make sure that we are not sending mixed messages to our constituents, i.e. the users of these drug products. So the NCCLS actually has invited me to become a member of the Antibody Susceptibility Testing Committee to provide our views on the breakpoints that we have established to try to assure that we are -- that we have the same kinds of breakpoints and that we are not sending confused messages to our constituents.

(Slide.)

Now I would like to discuss the kinds of microbiological studies that are submitted during the investigational new drug stage. The preclinical information required to aid in establishment under the provisional breakpoints is as follows: We require studies on the mechanisms of action. We need to understand the physiological and the morphological effects of the drug.

And, therefore, we need characterization of the targets the drug is likely to be affecting. This includes things like DNA replication, transcription, translation, biochemical pathways because this provides us an understanding of how resistance might emerge by changes in target side.

Now, clearly we know that there are other mechanisms of resistance which are important. And I will discuss those at a later time. We need to have a clear understanding of the antimicrobial spectrum of a compound. This activity that is the spectrum helps us characterize the potential clinical utility of the antimicrobial under investigation.

The susceptibility profiles are presented usually as histograms and population distributions. And these kinds of data help us assess where the breakpoints might be considered.

Now, as I tell you about the kinds of things that need to be submitted, you must understand that it is a compilation of all of these thoughts and all of this data and all of this information that goes into making or describing what would be the most appropriate breakpoint.

(Slide.)

Now, the mechanisms of resistance also aid in the establishment of the resistant breakpoint. Resistance mechanisms can limit the effectiveness of antimicrobials in clinical settings. Thus, we require characterization of their mechanisms and their distributions within targeted clinical populations.

The relationship of the increased susceptibility of these pathogens to the pharmacokinetics and pharmacodynamic parameters of the drug are assessed to determine probable breakpoints. Cross-resistance to drugs of either the same class or different classes mediated by different kinds of resistance mechanisms must be provided, again, to provide insights on the potential utility of the drug.

(Slide.)

Animal model studies are also very important during product development. They are used to assess the potential efficacy of the drug in either prophylactic models or in therapeutic models. They are used to investigate the nature of the disease process and how the product works against the specific diseases that are investigated.

They are also used the characterize the pharmacokinetics of the antimicrobial and to make decisions about the kinds of doses that should be used in humans. They also -- the efficacy aids in characterizing relevant pharmacodynamic parameters, also. These observations, again, provide additional evidence used in setting of the breakpoints.

(Slide.)

Now, pharmacokinetics and pharmacodynamic studies have been elevated to a greater degree of science in that we must have a good understanding of the absorption, distribution and metabolism and elimination of the antimicrobial, the serum protein binding which may affect the utility of the drug, and tissue distributions.

The tissue distributions are important because they allow us to assess whether sufficient drug is present at the site in relationship to the MIC of the organism that is being treated. This information and the animal model studies help us examine the relationship between the efficacy and the pharmacokinetic and pharmacodynamic parameters. These operations, again, provide additional evidence that is used in setting the breakpoint.

(Slide.)

Now, an example of pharmacodynamic parameters that are emerging from animals and limited human clinical studies are as follows: time above the MIC for beta lactim antimicrobials, it seems to be a pharmacodynamic parameter that is important. That is, the time the drug concentration remains above the MIC should be greater than 80 percent of the dosing interval to achieve successful clinical outcome.

For fluoroquinolones, the AUC to MIC ratio is important. If this value is greater than 30 for gram positive bacteria, for example, we have a higher success rate in terms of clinical efficacy or lower mortality.

(Slide.)

In summary, it is a compilation of data derived from different, but very related different types of studies which are used to provide insights into the activity of a drug and its clinical efficacy. This information is used to set the provisional breakpoints that is used in Phase 2 and Phase 3 clinical trials.

(Slide.)

Now I would like to talk about the information that is required for the new drug application. And basically what we want to establish is a correlation between the breakpoints that have been established and the provisional breakpoints that have been established during the investigational new drug stages and their ability to predict what happened in the clinical trials during Phase 2 and Phase 3.

So we are trying to establish a correlation between MIC results and clinical outcome. And that includes both bacteriological and clinical outcome. And this has an important aspect of the evaluation process because it validates what we have set provisionally as the appropriate breakpoints.

Now, the down side of this approach is that in essence we are only validating the susceptibility breakpoint because we only allow for inclusion in the evaluation of efficacy of a product organisms that are considered susceptible by the provisional breakpoint.

We really don't validate the resistance breakpoint. We rely on resistance mechanisms that are available to try to determine where that resistance would occur.

(Slide.)

Now, what is the purpose of susceptibility testing? I will have to leave you with these thoughts. Is susceptibility testing performed to predict clinical utility and outcome or is susceptibility testing performed to monitor changing susceptibility patterns in the emergence or resistance, or is it both?

The approach that you take -- or the philosophical approach that you take can influence the breakpoint that you establish. The debate certainly will not be settled in the near future because I can remember from microbiology back in my old days that this kind of question was continuously being asked. That concludes my presentation. Are there any questions?

(Applause.)

DR. BEAULIEU: Thanks, Al. Our next speaker is

Dr. Tom Shryock. Dr. Shryock has an advance degree from my alma mater, Ohio State University, which is unchallenged in its academic excellence, at least by anyone I am willing to listen to.

(Laughter.)

However, they have fallen on hard times on the football field lately and we won't go there. Dr. Shryock also has two post-docs in cystic fibrosis and pulmonary infections. He is currently the technical advisor in microbiology for Elanco Animal Health.

He has previously had experience in research and development of animal drugs at Pfizer Animal Health and he was an Assistant Professor at Indiana State University. He is also currently a chair-holder I think at -- on the NCCLS. And he is here this morning to talk to us about antibiotic breakpoints, methods for determining those and their use in the veterinary medical community.

Does anyone in the audience happen to have a laser pointer or know where there is one in the room? Thanks.

ANTIBIOTIC BREAKPOINTS: METHODS FOR DETERMINING AND USE BY THE VETERINARY MEDICAL COMMUNITY

Dr. Tom Shryock

DR. SHRYOCK: Thank you very much for that kind introduction, Andy. I appreciate being up here with fellow alumni. It is my great pleasure on behalf of the NCCLS to address you today on the Veterinary Antimicrobial Susceptibility Testing Subcommittee.

(Slide.)

And since time is limited, I am going to run through this fairly quickly as far as organization. If you want to check out the website, NCCLS.org, there is much more information about the organization. It is a standards and guidelines writing organization. Microbiology is just one of several components in clinical laboratories that this organization encompasses.

The NCCLS process itself revolves around a tripartite process of participation from the professions, government and industry. And it uses a consensus process to derive the documents that it produces.

With respect to the development of the AST, or antimicrobial susceptibility test methods, I would like to point out that the current methods are adequate for testing rapid growing organisms. And the list includes Enterobacteriaceae, Staph., Strep., some miscellaneous pathogens.

What is obvious by its omission and germane for this particular meeting is Campylobacter. There are documents that are available for human pathogens as well as for veterinary pathogens. In all of these documents, there are really two components as Al had outlined. There is a lot to do with quality control and methods including standardized procedures, QC. And these deal specifically with the MIC test and the auger dish diffusion test.

(Audio missing due to technical malfunction.)

And you can see here in this example of a single dose, there is clinical cures ---

(Audio missing due to technical malfunction.)

And the red line here would be the intended breakpoint for susceptible organisms. So what we would like to do is look at time after dosing to see if, in fact, we can achieve a concentration greater than that MIC. You can see in this example here an eight microgram per ml can be achieved for susceptible.

(Slide.)

Now, when we come to the scatter gram data set, MIC is listed on the left. Zone and inhibition diameters on the top side here. At this eight or less microgram per ml level, which was indication of a clinical success, you can see there is a large cluster.

So that would be where we would draw the line and say, okay, everything eight or less is susceptible. We go up one dilution for intermediate buffer zone. And then anything above that at 32 or greater would be termed resistant.

You will note also that in this susceptible population, there is a range of MICs from eight, four, two and one and so on. There is really no way to distinguish between differences in clinical outcome of those isolates with lower MICs versus those that maybe are a little higher. They are all susceptible in the eyes of the NCCLS as far as clinical outcome.

So in this particular example, this is what you would see in the document as far as how those breakpoints would be reported.

(Slide.)

Obviously, the establishment of the interpretive criteria are not without difficulties and there is lots of debates usually revolving around the correlation of these data points. The decreased susceptibility aspects here really have not been established for any agent at this point in time.

(Slide.)

There is lots of demographic discussions, controlled clinical trials versus community and animal disease models. Those all get factored in at some point or another. As Al mentioned, there are some ethical issues of treating patients, be they animal or human, with high MICs since you would expect clinical failure to result.

(Slide.)

With regard to Campylobacter testing on the methodology issues, Bob Walker at Michigan State is heading up a working group that has members from both the AST and VAST. And the objective here is to standardize the methodology, to define appropriate quality control strains, identify test media, etcetera.

The interpretive criteria ultimately to be set for treatment of Campylobacteriosis would have to fall into that AST realm since there are no veterinary antimicrobials that have a claim against Campylobacter. This would entail a specific sponsor presentation as it would for any other antibiotic or disease-causing agent to establish those interpretative criteria. Once the methods are available, they can be applied to epidemiologic purposes.

(Slide.)

So just to sum up here and get us out to the break, let me say that the interpretive criteria then are basically set on three different parameters: the efficacy, pharmacology and scattered gram or epidemiology data. There is as yet in the eyes of the NCCLS no approved methodology available for Campylobacter testing. It is being developed at this point.

And finally, the interpretive criteria which was validated for Campylobacter will need to be set by the NCCLS AST group, as well as the FDA upon appropriate presentations of data and determinations. So that concludes the remarks that I wish to make this morning. And I will open it up for questions.

(Applause.)

DR. BEAULIEU: Any questions for Dr. Shryock?

(Away from microphone.)

MR. : Doctor, how do you know where the issue is species-specific MIC ---?

DR. SHRYOCK: The question was how do we deal with species-specific issues given the fact that there is different parameters of absorption and metabolism, etcetera. Each sponsor brings forward that specific kind of data for the pharmacology in the target animal species for which interpretive criteria are being requested. And that is what makes this a real challenge and really sets the basis for the need to do this on an animal-specific basis.

For example, when we have a particular antibiotic that is used in two different food animal species, say beef and poultry, the sponsor needs to bring forward the relevant information for each one of those species. And the break points could be different between those different species because of the pharmacologic behavior of those -- of that agent in the two different species. They are different.

DR. BEAULIEU: Any other questions? We are running a little behind this morning. We got a late start. I would beg your indulgence in getting back here within 15 minutes. If that doesn't suffice, I would remind you that a long break equals a short lunch. I will see you in 15 minutes, folks.

(Whereupon, a brief recess was taken.)

DR. BEAULIEU: Take your seats, folks, so we can get started. Hopefully folks will join us almost immediately. Our next speaker is Dr. Kirk Smith. Dr. Smith has a D.V.M. from Iowa State, Ph.D. from the University of Georgia. He is currently Supervisor of the Food-borne, Vector Borne and Zoonotic Diseases Unit of the Minnesota Department of Health.

He was formerly with the Epidemic Intelligence Service at CDC. Dr. Smith is going to speak to us today about epidemiology of Campylobacter in humans.

EPIDEMIOLOGY OF CAMPYLOBACTER IN HUMANS

Kirk Smith, D.V.M., Ph.D.

DR. SMITH: Thank you. And good morning. This is kind of a daunting task to cover this topic in ten minutes. So bear with me if I speed through some things.

(Slide.)

Well, Campylobacter is the most commonly recognized cause of bacterial gastroenteritis in the United States. It is estimated that there are about two million symptomatic infections per year which is a figure you will see in the risk assessment. And this corresponds to roughly one percent of the United States population.

The most commonly identified species of Campylobacter among clinical isolates from humans is C. jejuni which accounts for 95 to 99 percent of the isolates. Most of the rest are Campylobacter coli which is clinically indistinguishable. So when you talk about the epidemiology of human Campylobacter infections, we are talking primarily about C. jejuni.

(Slide.)

Campylobacter jejuni is found worldwide. As in the United States, it is very common in other industrialized countries. It is actually hyper-endemic in developing countries. And most children will experience multiple infections by the time are a few years of age. And so it is not common that Campylobacter is a commonly identified cause of traveler's diarrhea.

(Slide.)

We will get more into the clinical signs and symptoms later. But Campylobacter causes diarrhea, often with fever and cramps and often with bloody stools. The incubation period can range anywhere from one to eight days. But it is typically three to four days. It is usually a self-limited illness. But it can cause serious invasive illness, particularly in the elderly, infants and the immunocompromised.

(Slide.)

Just to mention FoodNet briefly. Some of you I am sure are familiar with it. It is a collaborative agreement between these federal agencies and certain state health departments.

(Slide.)

And these are the FoodNet sites currently that cover a population of about 20 million people.

(Slide.)

And FoodNet does active surveillance for a number of bacterial pathogens including Campylobacter. And it does surveillance for parasitic organisms, syndromes related to food-borne disease and also food-borne disease outbreaks.

(Slide.)

Well, based on FoodNet data, again, Campylobacter is the most commonly recognized bacterial cause of gastroenteritis among the FoodNet sites. And you can see it is consistently so each year.

(Slide.)

And this graph shows the seasonality of Campylobacter infections in this country. And typically what you will see is a marked upswing in cases during May or June and then a peak in July and August and a steady decrease throughout the rest of the year.

(Slide.)

And this graph is Minnesota data, just a little different way of showing the same thing, the summer seasonality of Campylobacter infections.

(Slide.)

Well, this graph shows the age distribution of Campylobacter cases. By far the highest incidence is in infants where we will see an incidence of greater than 50 cases per 100,000 people. Children less than five years of ago also suffer a fairly high incidence, not really demarcated on this graph.

We see a second peak in incidence amongst young adults 20 to 30 years of age and to a lesser extent 30 to 40 years of age.

(Slide.)

Well, almost all human Campylobacter infections are accounted for by these sources, poultry, unpasteurized milk, inadequately treated surface water, pets and foreign travel. The specific sources of infection during foreign travel aren't really known, but are very likely to be the other sources on this list.

(Slide.)

Well, poultry is by far the most important source of Campylobacter for humans. In most surveys, you will find that 50 to 80 percent of retail products are contaminated. And poultry accounts for roughly 50 to 70 percent of sporadic human infections with Campylobacter. And this is a figure that you would also see in the risk assessment.

In evidence from throughout the world including some work we have done in Minnesota, it is apparently that poultry is a source for fluoroquinolone-resistant Campylobacter for humans, as well.

(Slide.)

This table shows outbreaks of Campylobacter that have occurred in the United States from 1978 to 1996. And first let me say that outbreaks due to Campylobacter are rare. You can see an average of about six per year in the whole country. And when they do occur, you can see they are food-borne or water-borne. The specific source for many of the food-borne ones is actually unpasteurized milk.

You can see poultry isn't implicated specifically in many outbreaks, but many of the other food items that are linked to the outbreaks have actually been cross-contaminated with poultry in the kitchen.

(Slide.)

The seasonality of outbreaks due to Campylobacter is different than the seasonality of sporadic cases. Again, sporadic cases, seasonality in the summer outbreaks. The seasonality tends to be in the spring and in the fall. And this is due to largely to the seasonality in outbreaks due to unpasteurized milk shown in yellow and due to inadequately treated water in blue.

(Slide.)

Okay. So just a brief summary. Summer seasonality. Sporadic cases are -- account for the vast majority of cases, are far more common than outbreak-associated cases. Sporadic cases occur for 99 percent of all Campylobacter cases.

Poultry is the primary source of Campylobacter for humans in the sporadic cases at least. And person-to-person transmission of this organism is rare. For some reason, we -- it just doesn't appear to be very efficient. We don't see the institutional outbreaks. We don't see the day care outbreaks that we do with some other pathogens such as Shigella and E. coli 0157:H7.

(Slide.)

Okay. Back to clinical features. Infection with Campylobacter can range from no signs whatsoever, it can be asymptomatic, or it can cause death. Diarrhea is a hallmark, of course, and it is often severe, often producing bloody stools. Fever can occur. Abdominal pain, severe abdominal pain is another hallmark of Campylobacter infection. And the nausea and malaise occur commonly, as well.

(Slide.)

Now, Campylobacter gastroenteritis is usually self-limiting. The duration is usually less than a week, although it is a pretty miserable existence for a week. It is a debilitating illness.

The duration can be up to three weeks in 20 percent of cases. Systemic infections are rare. Most isolates are from stool. Only about 0.5 percent of isolates are from blood. And the hospitalization rate for confirmed Campylobacter infections is about ten percent, ten or 11 percent. And that is really a fairly high figure when you think about it.

(Slide.)

The case fatality ratio from a couple of outbreaks is three to 24 per 10,000 cases. And it is estimated that there are 100 to 150 deaths per year in the United States. And Campylobacter not only causes gastroenteritis, but it does cause some chronic sequelae including reactive arthritis and Guillain Baret syndrome.

(Slide.)

So antibiotic treatment for Campylobacter gastroenteritis is not needed in most cases. It is beneficial to patients with prolonged or worsening symptoms, high fevers or bloody stools. And it is definitely indicated for patients who are immunocompromised or pregnant. This is very important. Our immunocompromised population is going to do nothing but grow as the baby boomers age.

(Slide.)

So the drugs of choice for Campylobacter when treatment is indicated are either erythromycin or a fluoroquinolone such as Ciprofloxacin. And fluoroquinolones are used widely for the empiric treatment of gram negative bacterial enteritis. And it is also a treatment of choice for traveler's diarrhea.

And so where as both will work fine on Campylobacter, erythromycin actually is not effective for the other causes of bacterial gastroenteritis. And that is what causes a problem for physicians, is Campylobacter needs to be treated early. And so treatment needs to be started before culture results are back.

(Slide.)

Just quickly, a little bit about NARMS on the human side. Just quickly, Ciprofloxacin resistance was documented in 13 percent of Campylobacter infections both in 1997 and '98.

(Slide.)

I just quickly want to tell -- this is the work that we had published in May. I do have reprints of this article for anybody that is interested in catching me during the next two days. But quickly, in that we show -- and these are the data -- the data from 1998 are what is in the paper. These are the percentage of _Campylobacter_ isolates submitted to the Minnesota Department of Health that were resistant to quinolones.

In red are the yearly figures. In blue are the quarterly figures. In 1998 -- that is as far as we got published, the yearly data, the yearly percentage resistant was ten percent. In 1999, now, of course that is not counting December yet, but things won't change much. But not counting December, the yearly percentage resistant is over 17 percent now.

And you can see during the first quarter, 39 percent of isolates were resistant. And even during the trough in the third quarter of this year, over ten percent of isolates were resistant.

(Slide.)

And this is in the paper, so I won't belabor it. But we did show a clinical effect. Quinolone resistance did result in a longer duration of illness for patients that were treated with quinolones.

(Slide.)

And we did isolate Ciprofloxacin-resistant _Campylobacter_ from poultry and -- quite commonly and showed identical DNA fingerprints in resistant isolates from chickens and domestically acquired resistant human cases.

(Slide.)

Okay. And that is my whirlwind tour. And I will stop there. Thank you.

(Applause.)

DR. BEAULIEU: Maybe one question for Dr. Smith. Tom?

(Away from microphone.)

MR.   : Yes, I was curious to see if your number graphics supplied --- less --- evidence --- particular segment of the population --- Campylobacter?

DR. SMITH: Well, absolutely. I really don't think a lot of it comes directly from eating raw or undercooked poultry. I think most people know not to eat undercooked chicken.

What I think is happening is I think the vast majority of Campylobacter infections from poultry actually comes from cross-contamination in the kitchen of other food items, food preparation surfaces, utensils and so on and so forth. So that would be my best guest.

DR. BEAULIEU: Thank you. Our next speaker is Dr. Paula Cray. Dr. Cray has a whole series of degrees associated with microbiology, bacteriology, biochemistry, veterinary microbiology. She is currently the Research Leader of the Antimicrobial Resistance Research Unit at USDA's Agricultural Research Service at the Russell Research Center in Athens, Georgia.

She has a great deal of experience dealing with food-borne pathogens, particularly Salmonella and Campylobacter. And she indicates that one of her other interests is she is also proficient in fast foods. And she and Dr. Sundlof might want to compare notes there because I know he is an expert at McDonald's.

EPIDEMIOLOGY OF CAMPYLOBACTER IN ANIMALS

Dr. Paula J. Fedorka-Cray

DR. FEDORKA-CRAY: My fast food expertise is dependent upon which toy is out.

(Laughter.)

Well, it looks like I have to re-boot the computer. It put itself to sleep. So I will take a moment to say that I will stick with the thought that Andy gave earlier that developing gray hair is a result of a antimicrobial resistance. I keep trying to tell my children now that this is the professional look.

And I caught them on a telephone conversation recently telling my mother that a bottle of her Clairol would fit really well in my stocking this year. I am not sure where that is going to leave me. I hope it is a good color. I guess I could get purple to match my computer, too. I saw a few of those in Paris last week.

(Laughter.)

Well, with this modern technology, I had modern technology glitches in -- this week when I left my power cord on Monday at home and found out that you just can't plug your finger into the socket.

(Slide.)

I will start by saying that some of the production statistics, just to give you a background on where we are coming from, 8.25 billion chickens were -- are estimated to be in production for 1999. And more than 29 billion pounds of ready-to-cook chicken is produced. This results in an economic impact of 22 billion dollars for the wholesale value of these shipments.

We eat it is projected more than 79 pounds of chicken per year per individual. This is increased from 28 pounds per person in 1996. And our estimated expenditure for these products is 40 billion dollars. A retail price for chicken has increased from really a minuscule amount to $1.02 per pound.

However, it is supposed to be 44 percent less than it was many years ago, though I don't seem to think that the IRS has much thought about that. And I know my sons who consume vast quantities of food have no consideration for what anything costs anymore.

(Slide.)

There are top states for producing chickens which sometimes results in a regional analysis. And broiler companies directly employ 300,000 Americans. Now, if we look at Campylobacter itself, I was pleased to see that Kirk really gave a lot of the epidemiologic aspects. So I will concentrate a little bit more on the microbiologic aspects.

It is a fastidious organism. And really, it is fairly fragile compared to something like Salmonella which can survive in the environment for years at a time and survive in many different means and states.

However, it has been demonstrated that Campylobacter can survive for weeks in soil and water. I don't think that it has been clearly demonstrated that Campylobacter can survive for a very long period of time on surfaces. And we don't find that surface survival even in the laboratory is very high. And I can assure you that OSHA doesn't want to come on a daily basis to the lab and check the bench tops.

It is a gram negative organism which makes it one of the more popular organisms. It has a motile nature which helps us in identification. And it has special oxygen requirements in that it requires a low oxygen, a micro-aerobic environment for growth. So this confounds and compounds our problems in the laboratory as we try to propagate it.

It often requires special media including the addition of blood and blood products, iron and other compounds for growth. Over-growth is highly likely, in fact almost -- most often observed on a daily basis regardless of what one puts into the broth media for selection. And this confounds our selection of Campylobacter.

And often it is missed. So I will still comment from Dave Nesbitt who gave a comment at our USDA/FSIS meeting earlier this week when he said that they noticed 80 percent prevalence in swine. And someone said, "Oh, you are doing well. You only missed 20 percent."

So the range for prevalence estimates go anywhere from zero to 100 percent. And I think that a lot of that has to do with selection methods and skill of the lab itself. Antibiotics are often required to minimize the overgrowth in the media.

And this may effect recovery of some of the organisms. And --- gas that is used in media often as a selector. And it may select specifically for jejuni and coli populations which may minimize the prevalence of some of the other serotypes.

(Audio missing due to technical malfunction.)

--- you will find halviticus coming from cattle --- is why don't we see it for three weeks. Okay. Why is it so difficult then if it is there and we have the genetic relationship from the breeders to say that, in fact, it went from the breeders to the chicks but we don't see it for three weeks? What is happening?

And we have a lot of different theories about that, but that is a hot and heavy topic right now for scientific pursuit.

Now, one of the things though that we do observe is that within a single bird, we can see mixed species. And they are often recovered in varying numbers. We can have coli and jejuni, lari, maybe some --- all coming from the same bird. And it is hard to predict in what population it is going to be, although of course most often it will be jejuni or coli predominating over the other lesser species.

Mixed species have also been recovered from human fecal samples. And this then puts the question of our selection criteria for any one colony on a plate. If we are looking on a plate, typically -- because I have my nice new little purple computer, I failed to put all of my nice little pictures on here.

But if we look at a plate of microbiologic media and we have, in fact, the opportunity to pick multiple colonies from a plate, which one are we going to select. And this can be confounded by the culture methods and by the fact that we have this mixed population and it is difficult to predict exactly what is coming from any one individual source.

(Slide.)

Now, although we have this mis-population, it is often confounded by our culture methods, as we said. And if we look to genetic identification to do rapid PCR tests, for example, while it can provide us with information about the mixture, it doesn't provide us with an isolate to do any further characterization. So that's what limitations we would have in using genetics to identify what is in a population.

So then if we finish us looking at slaughtered, all of our populations are, in fact, mixed then in the chill tank in particular. And there is a high probability that, in fact, the carcasses will acquire other strains while mixed in this fecal soup. And we are the premiere lab for ---

(Audio missing due to technical malfunction.)

And these mixed populations that are observed in slaughter samples then, we have to ask ourselves from the scientific standpoint what are these differences between the strains that might be coming from any --- of each individual isolate and with respect to the resistance profiles that may or may not be identified from the selected isolate.

And then we have to ask ourselves then how do we facilitate selecting an isolate. Many members from the laboratory are in the back. To them I owe great deal of thanks. We have had many pizzas over the year, increasing from 1,000 to 5,000 colonies is to integrate my budget there along the pizza lines. So the Pizza Hut will be happy.

So these are some of the questions I think that we have to ask ourselves scientifically. If we look at some of our information, we see that just by random chance, 33 percent of our isolates that we selected over the course of the year were coli as opposed to jejuni which suggests that there is a higher population of coli actually going into the human population.

(Audio missing due to technical malfunction.)

--- associated with jejuni. We do see a much higher resistance with coli compared to jejuni for both the human and poultry isolates. And I will leave you with that.

(Applause.)

DR. BEAULIEU: I quick question for Paula?

MS. : In Europe, we see the same seasonal peaks that you have shown in your material in the U.S. But you also see the same seasonal peaks in the poultry. The thing is that the human peaks ---

(Audio missing due to technical malfunction.)

DR. FEDORKA-CRAY: What we do is seasonal association with Campylobacter also in the poultry production, although this may, in fact, be confounded by region in that we have different climactic areas that we would be dealing with. So the prevalent --- region for any number of reasons.

And then we can -- we have observed some studies which we have been involved with in which there really wasn't much of a seasonal analysis or, in fact, we do find times that it shifts. And those may be due to climactic reasons.

One of the things that Norman Stern has reported on is that when there is a more -- more rain or humid conditions, then the prevalence of Campylobacter increases. So even though you see you may have an off season when you shouldn't be seeing it, say winter, if it a rainy winter that is a little bit warmer, then I would guess that the prevalence of Campylobacter, in fact, may be higher at that point in time. So --

DR. BEAULIEU: One last quick question.

(Away from microphone.)

MR. : A comment. Relative to chillers and in poultry processing plants, the additive of fecal soup, as a veterinarian working in this industry, I feel that that is the thing. That the chillers are mostly after ---, after the food separation of the carcasses, after at least one, two, three --- antimicrobial compounds.

And I might add that there is a zero tolerance for fecal material in chillers established by USIS. And I know of plants --- chillers. If you think this is a small task for simply a chiller that holds thousands of gallons of ice water, let me tell you it is not. So I am taking some exception.

DR. FEDORKA-CRAY: And you are right --- for colony on that. And I should not have mentioned it as fecal soup. I think that when you look into that, you will see a lot of carcasses. And a better description would be that all the carcasses are in close contact with one another and have the ability -- a lot of the Campylobacter contamination does occur on the skin and skin surfaces.

And so the opportunity for mixing and rubbing is there. I meant in no way to imply that they were standing in a lot of fecal soup.

(Away from microphone.)

MR.   : Well, even as a --- chiller --- agitated ----.

DR. FEDORKA-CRAY: Yes.

MR.   : --- by air. Yes, their contact where there is also separation where the ice and the warmth completely surround the carcasses. But the question I have -- and I saw this in the document that you have just given us. I see here it is referenced where we ---

DR. FEDORKA-CRAY: Right.

MR.   : --- as literally an enrichment for growing Campylobacter. Now, when do you do that? Aren't we actually selecting the first stage of development of resistance for ---?

DR. FEDORKA-CRAY: There is a debate about that. And we have talked about that with CDC. We are looking at some of those mechanisms. I think that -- let's see, Nina, do you want to speak to Gerald's -- I think Gerald feels that there is no selection, is that correct, as far as there is no genetic selection ---

(Audio missing due to technical malfunction.)

--- for isolates that are more prone to that first step because they will have to have some resistance to the nalidixic acid to propagate. And there is a disparity in methods in how isolates are selected. And that --- you know, and if that is in fact the case, then all of these graphs and everything have to have a disclaimer associated with it.

We don't use it for our selection purposes. It is an identification tool. But other labs will.

DR. BEAULIEU: Thanks, Dr. Cray. I am sure Dr. Cray will be around for your other questions. I am sure she will be happy to answer those one on one. There is also time set aside this afternoon for additional questions. Go ahead, David.

Our next speaker is David Vose. David is an independent risk analysis consultant currently located in

France which I think falls into the category of it is a tough job, but somebody has got to do it. He is an expert in --- risk analysis with ten years experience in simulation modeling. He has applied his expertise to a wide range of problems from oil and gas production to banking to epidemiology all over the world. And David is going to take us through the risk assessment.

PRESENTATION OF CVM RISK ASSESSMENT

Dr. David Vose

DR. VOSE: Thank you. Good morning.

(Slide.)

The CVM risk assessment, what I am going to try and cover in the 40 minutes that I have got is, first of all, what we modeled and why, the logic associated with that model. And I am sure that that appears to something of a black box to at least a few of you.

I am going to talk the results that we have gleaned so far, uncertainty analysis which is a large part of what we have been doing, recognizing the degree to which we do and don't know. And as Wes pointed out in his presentation, that a great deal of the value of risk analysis is to work out what it is you know and don't know.

And I am also going to describe how one might use the model in brief form to help make your regulatory decisions.

Well, first of all, of course, I have to recognize the team that I have been working with. First of all, Sharon Thompson who is my boss so she comes at the top of the list. Sharon took over with this project halfway through from Peggy Miller. And I take my hat off to her because that is a tough job to do. It is halfway through and she suddenly has got to understand what we have been doing. And it was a very complicated problem that we had to deal with.

I also have to thank Peggy Miller who was the initiator of this project. And I have to recognize to Peggy that she was the person who originally thought of this approach to assessing this risk, as much as I would have liked it to have been me. I simply executed what was a very clever idea from her.

There is me, the consultant, of course ---. Kathy Hollinger -- just in case you don't know because you will end up in the wrong place if you don't know that, somewhere in Germany.

(Laughter.)

Okay. Kathy Hollinger, as Dr. Sundlof has said in his opening remarks, Kathy put an awful lot of effort in. And she sort of reminds me of a bulldog. I am British. And so she has the tenacity of the bulldog who will go out and just keep collecting information and not be satisfied. She would often come up with a comment to me, "But it is not that simple, David", which gets very irritating because I would like it to be. It's a model. But all power to her. She kept me on line.

As did Mary Bartholomew who spent a lot of time helping collect the data and analyzed the data that was given to us in forms that weren't necessarily exactly what we needed. In quantitative risk analysis, you need numerators and denominators very often because you want to work out uncertainty.

People will tell you, "Oh, well, we found 30 percent resistance." They don't like to tell you that they only checked five chickens. So we need numerators and denominators if we are to say what that means. And Mary has done a great deal of helping obtain that information.

(Slide.)

Okay. This is the only slide with this much information on it. So I apologize. Why do we model fluoroquinolone-resistant Campylobacter in chickens? Well, this was originally set up as a pilot study to determine the feasibility of doing the risk assessment on antimicrobial, bacterial, blah, blah, blah.

We wanted to look at the data needs that would incur and we wanted to look at the source of information where we may be able to find that data. As others have pointed out, Campylobacter is the most commonly known cause of bacterial food-borne illness in the U.S.

Ninety-nine percent of Campylobacteriosis are sporadic illnesses which makes life a lot easier from a mathematical point of view. If they were these outbreaks, then we would have a more difficult problem.

Chicken is, as others pointed out, the most commonly identified risk factors for Campylobacteriosis in the U.S. It has been -- Campylobacter has been reported to develop resistance quickly to fluoroquinolone which, again, makes our problem much more simple. Fluoroquinolones are important antimicrobials, of course. It is a valuable drug to us and we want to make sure that we guard the value of that drug.

And most importantly, we felt that certainly as we started to move along this part, we felt that there was enough data in order to produce a meaningful quantitative risk analysis. I am a quantitative risk analyst. I am involved in the mathematics of things.

Another option is to go down the qualitative route where you just simply identify the factors and talk descriptively about the problem. And other organizations have done that.

(Slide.)

Okay. Well, this risk assessment modeled direct transfer of resistance because fluoroquinolone resistance is on the chromosome. It is not transferred to other bacteria. This is something I know absolutely nothing about. But because it is not a two-step process, it makes, again, our mathematics a little simpler.

You can see that we have picked out this particular problem for two reasons then, Campylobacter fluoroquinolone resistance in chicken. A) Because it is a big issue. But B) because there is data there. And C) the math makes it feasible.

Now, we are going to try some further analyses on the risk initiatives underway to look at other microbial resistance issues such as indirect transfer. That may or may not be something that we can feasibly do quantitatively. But we are certainly not going to start out saying yet we are going to be able to do everything else quantitatively because we could do this one so.

But -- so the point to take away I suppose here is that if we couldn't have done it quantitatively on this risk issue, we certainly wouldn't be able to do it on the others. But we can, so we have got some feeling of security that we can proceed on.

(Slide.)

Okay. The problem we modeled, imagine you have poultry in a shed. They get some disease, e.g. collibacillosis. I probably said that wrong. They are all treated with a fluoroquinolone. Then that fluoroquinolone-resistant Campylobacter, it proliferates in the drug because -- sorry, proliferates in the poultry gut because all of the other bacteria have been erased.

Then us humans go and eat that chicken and they get contaminated with that Campylobacter. And then they go to the doctor and the doctor says, "Oh, you are ill. Take some fluoroquinolone." And nothing happens. So to how many people would that occur is what we are trying to work out.

Now, there will be a lot of people I think who would criticize this model because it is not a predictive microbiological model. A predictive microbiological model would say, for example, look at the number of pathogenic organisms in the chicken and then flow through, see how many were gotten rid of in chillers that the gentleman in the back was talking about through evisceration, etcetera, etcetera.

How many would be lost through natural attenuation of the numbers from chilling or freezing, and then the cooking. And, oh, it just goes on and on. I mean, you can think of so many things. Even if we just dealt with the one last issue. Here is a quantity of chicken that has fluoroquinolone-resistant Campylobacter on it and you go feed it to someone. Well, who do you feed it to. You know, if I gave all of you out here the same dose with the same pathogenicity, you would have varying reactions.

There would be any number of you who would have light illness. Some would have no effect at all. And it would depend on, for example, what you had -- when you had your cup of tea, did you have some yogurt if there was any out there? Did you -- have you had a full meal? Have you had nothing to eat yet this morning like me, etcetera, etcetera.

So it is an extremely complicated problem if you want to look along the microbial part. And certainly from the point of view of the regulator, the Food and Drug Administration here, it really wasn't relevant to look at all of those parts.

Now, from the point of view of industry, I can quite imagine that they would want to work out ways that they can try to reduce the number of bacteria that actually were loaded in their chickens. Absolutely right. It is fair to say is it fluoroquinolone that should be used or should we try and work out ways of reducing its use; is there any effect on the chicken population. Right.

(Slide.)

So we chose this rather simple model as being the most appropriate. Now, although it is simple, we can make corrections to the original assumptions for changes in the system. For example, if changes in human feeding patterns -

- if we eat more chicken or less chicken or if we tend to eat it more cooked or less cooked, things like that. We can probably start making some kind of fudge factors, but reasonable guess fudge factors that will allow us to update our model as the system changes, if it does.

But the essential real benefit of this is it provides a responsive means of continually assessing the risk. By responsive, I mean if we keep monitoring the problem, we can assess month by month or quarterly by quarterly, we can assess the size of the risk.

Now, if we had gone down to a predictive microbiological model with so many changes to the system like they change the number of chillers that they use or the frequency with which they clean them out, well, we would have to go all the way back and do a much more complicated analysis.

So the point of this is it is easy to use. And we can get a quick idea of the size of the risk that we are exposing the U.S. population to.

(Slide.)

Okay. Now, to my mind, this risk analysis -- this microbial risk analysis is unique in that we found data to quantify all the model parameters. I say unique because I have been involved in a number of microbial risk assessments including the United States of America. And almost always

-- well, always we have somewhere along the line to make a guess. We have to assume something that we really wouldn't like to have to assume. We have to use a surrogate bug for the dose response, etcetera, etcetera.

Well, in this particular risk assessment, we have thanks largely due to Kathy and Mary found data to quantify every single parameter. And that data has come from a number of sources, from FoodNet surveys, physicians' reports, CDC's attempt at a case control study, NARMS, from poultry industry, data on consumption and production, U.S. population records, etcetera.

Data didn't just have to be collected, but it had to be collected in a form that allowed us to perform uncertainty analyses. So we had to dig out not just the information like prevalences and percentages. But we had to, as I said before, talk about numerators and denominators.

Now, given all of that, 1998 was the first year that we were able to produce a complete set of data. So we had both sides of the equation that I am going to talk about in a minute, we had data for everything. What I had originally imagined doing and I had hoped that we would be able to achieve is to compare several years of data from the past. And we would get a much more firm understanding of what was going on.

So I suppose at this point we are in the first year of what I hope will be several years of data collection that will make us more and more able to understand the connection between Campylobacter-resistant fluoroquinolone in chickens and the effects on the chickens.

(Slide.)

All right. If you read through the risk assessment report that we have done, probably a lot of you will be confused about this quantifying uncertainty. Uncertainty is about the state of our knowledge. There is in theory some parameter value that is out there that could be known. But we will never have perfect data. We will never have perfect information about that parameter.

And if we just take at face value some of the data that we have when we have a very small amount of data, we can be very wrong. We can be overly conservative. We could be overly pessimistic. We don't know. But we would be very wrong if we just take the data at face value.

If I toss a coin three times and I get two heads, you are not going to tell me that the probability of the heads is 66 and two-thirds percent. It wouldn't make sense. Well, that is the same principle.

In this particular problem -- analysis, we used a Bayesian approach. And there were good reasons for that. First of all, it allows us to combine dissimilar data. So we were able in a couple of instances to take a set of information over here with a particular certainty with information involved in both of those two different studies.

A potential criticism of the Bayesian analysis is that we have to introduce something called a prior distribution. And that would introduce a very small bias. And Dr. Cox, who is following me here this morning, will probably mention that being a Bayesian mathematician.

But having said that, the data set sizes mean the results pretty much equate to the classical statistics estimates which is perhaps the things that you remember from university and certainly less controversial, although Bayesian inference is certainly growing in use.

(Slide.)

And so quantifying uncertain analysis not only tells us how much we really know and how good our predictions can be. But it also tells us where we should be able to collect more data and how it would be useful.

(Slide.)

So here is an example. This is a distribution of uncertainty about a particular probability. And you have -- I'll get my laser pen here. You have three distributions here. The first one, which is this broad curve here, is talking about your estimate of a probability.

If you were, say, to take -- go to a population and say -- oh, let's talk about Republicans and Democrats -- ask four people, "Are you going to vote Republican or Democrat?" -- and I can do that because it is 50/50, so I am all right. Two say Republican and two say Democrat.

Well, if I am trying to extrapolate to the true population, I know that I don't really know very much about the proportion of people that are going to vote Democrat or Republican. And so this description here is describing the amount of uncertainty.

Well, it is pretty much somewhere between zero and one, not very sure. But as I accumulate more data, I go through this -- the beta (3,3) is talking about four people, two of each side; a beta (11,11) is 20 people, ten on each side. And you can see my distribution is becoming a bit narrower.

And then here we have got a beta (21,21) which is 20 people of each side. So 40 people are asked and 20 people said Republican, 20 Democrat. And there you have a much narrower level of uncertainty. So the point of it is that if we accumulate more data, so we become progressively more certain about what the truth is out there.

(Slide.)

For those of you who are more technically inclined, here is a little graph to show that although Bayesian inference has a slight bias to it, the classical statistics of an estimate for this particular type of problem, when you had four people, two Republicans and two Democrats, well, the classical statistical estimate will be this thing here, this red line.

It is a binomial distribution. And there is an approximation there in blue which is the normative approximations of the binomial versus this green line which is the Bayesian estimate.

Well, what I am trying to show here is that with this red step line, that is the perfect classical estimate as they call it. And yet they frequently represent that with this blue line. It is a little more helpful for them for a majority of the analyses they do. So if a classical statistician is willing to take this step line here and make it into a blue, then going from blue to the green, that is not a big deal.

(Slide.)

More importantly, as your data sets become bigger, so the difference between this three of them, and you can't see the blue and the green, the classical versus the Bayesian. They just completely overlay on each other. And that is not even for a very large number of data points, just 20 data points.

(Slide.)

So there isn't really any controversy between

Bayesian and classical inference in this particular model.

(Slide.)

Okay. Now, I do -- the difficulty that people will have I think in understanding what I have tried to d here is looking at this idea of a nominal expected number of people who will come out with Campylobacteriosis. I say nominal because I wasn't really very interested in the actual number of people.

CDC put a lot of analysis into trying to determine the true number of people out there in the population of America who got ill. Well, I was more interested in something called the intensity of that system because I want to know whether if we were to take that same number -- that same system and one year we note that 30 people became ill.

Well, the next year we are not going to note the same 30 even though there was the same risk out there. Maybe it is going to be 35. Maybe it is going to be 25. I want to know that if you were able to repeat that year many, many times, what would the average be which is my much better estimate of the true risk to the human population.

So here is an example of a Poisson distribution which is the appropriate distribution in this circumstance. And you can see, I have got -- this is the probability. And for a given intensity -- this is for a given size of risk if you like. On average risk, two people per year would die, whatever, ill.

Then you would see we could quite easily have zero people one year or we could have one person or two persons or three or four all with the same amount of risk. And yet we can observe different things from one year to another.

And that gives you some idea that we should be a little bit cautious about interpreting changes, reasonably small changes from one year to the other in what we observe in the illness out there because it could simply just be a sampling error. It is just that we -- it's just there is so much randomness out there, it is quite possible you will have a small sample one year and a larger one for the other, and yet have the same level of risk.

So I am very keen that when we do this risk assessment, we use it to quantify the risk. But we should be completely cognizant of the randomness that is out there that could if we are not careful sway us from making overly cautious decisions or underlie cautious decisions. And the purpose of doing the uncertainty analysis was to stop us from doing that.

(Slide.)

Okay. Model overview, how I set this model up was, first of all, to look at the number of Campylobacter culture confirmed cases observed in the U.S. population. And this comes entirely from CDC data except that I am interested in the nominal expected number.

So I am interested in that two value if you like from that Poisson distribution versus the actual observed numbers. So I am trying to get a sense of how many people out there are getting those Campylobacter cases.

And from there, this is in Section 2, I am looking at the total number of Campylobacter infections in the U.S. population. So it is the total number of Campylobacter infections in the U.S. rather than those that were culture confirmed cases because culture confirmed cases are the only ones that you actually observe in your health system because they have to be identified. You have to get them, thus, in scooping the poop and doing the microbial analysis.

So we extrapolate from there to work out the total number of people that are ill in the population. In Section 3, I am looking at those -- the number of those people who would have been ill from the fluoroquinolone-resistant Campylobacter because, clearly, those are the people who would be at risk.

And I want to see how many of those who were infected with the fluoroquinolone-resistant Campylobacter then went to the doctor and were prescribed an antibiotic and that antibiotic happened to be fluoroquinolone because, clearly, those are the only people out of everyone that had Campylobacteriosis, those are the only people who are going to have any observable difference in their final outcome.

Over here in Section 4, I am looking at the number of -- the quantity of meat consumed, of chicken meat consumed that is contaminated with fluoroquinolone-resistant Campylobacter. And the idea is to say if we take the Poisson intensities if you like of those two things, we can correlate them together in a sort of generic dose response model.

And with a constant of proportionality, we can estimate or we can relate the human health cases to the chicken. So Section 5 deals with how we go about making that connection.

(Slide.)

Okay. So let's deal with Section 1 quickly. In a fairly simple analysis in Section 1, I simply took the U.S. population data down here. I worked out the -- we had data for the number of observed and invasive cases from FoodNet, etcetera. I put that through.

This is uncertainty for about a Poisson intensity. And we simply extrapolated that out to a population. And then we split it between those that would have enteric and non-bloody, and enteric-bloody infections.

(Slide.)

In Section 2, we were looking at -- all right, the only people that you observe are those -- who were culture confirmed cases. So we missed a lot. We missed lots of people. If I go from the bottom, we missed those people, for example -- let me see, which way should I go -- well, we've got the number of people who sought care. We have the number of people who submitted a specimen. We have the number of people for whom the specimen then tested positive.

And so only those people who went through all of those chains actually ended up being observed in your FoodNet data. So we need to extrapolate back and divide by all of those proportions, all of those probabilities if you like, to work out the total number of people who truly were -- who had Campylobacter.

(Slide.)

And if we do that, I have -- this is a distribution where on the vertical axis I have a description of relative uncertainty, so -- confidence if you like. And you see the value range. In this case, we've got values that range from, say, about 0.9 million up to about, say, 4.8 million.

If you look at this on the cumulative frequency curve where this vertical axis here means the probability or my confidence that the true value is less than or equal to whatever the X axis value is. So, for example, I can read off here that I am five percent sure that the value is at least 1.3 million or something like that. And over here I am 95 percent sure that the value is less than, what would that be, about 3.8 million or something like that.

And over here on the bold line, I have the CDC estimate of the actual number that were observed in 1998 and -- which it rather fortuitously I suppose turns out to be at around about the 50 percent mark. So CDC and our data agree which isn't surprisingly because we used their data.

Now, I would like you to bear in mind that you shouldn't see this as the actual number, the distribution as the actual number of people. I know this is a difficult concept to get. But it is not distribution of the actual number of people uncertain about that.

It is the distribution of the intensity which has more uncertainty because we are taking into account the fact that we have a small sample from what really might have been out there. If we repeated that year, we could have seen different values occur from one year to another.

(Slide.)

Okay. So in Section 3, we are interested in those people who had those Campylobacteriosis cases who would not have benefitted from -- would have sought care and who would have received through it fluoroquinolone, but then obviously it didn't work. So we have to go -- we have to back through here. We take the number of people and then we work out those -- the proportion that relates to domestically consumed chicken because, of course, the fluoroquinolone we are interested. The administration is to domestic chicken.

And then we look down here at those who went off and sought medical care, those who were treated with some medication, the proportion of those who sought care and were treated with medication for which that medication was actually fluoroquinolone.

And then by calculating by taking the total number of Campylobacteriosis cases and dividing by all of these, we multiplied by all these probabilities or proportions. We ended up with estimates of the total number of people who would have had invasive infections and were treated, but unfortunately treatment didn't help them because fluoroquinolone was of no benefit and those who had enteric bloody and enteric non-bloody infections.

(Slide.)

And I have distributions here describing our uncertainty about what those values are. Again, these are Poisson means, intensity and uncertainties. And you see here we have got the confidence that the true number of invasive cases. Well, in 1998, it would be somewhere between, say, ten and 30. And there is the distribution.

It shows -- the back square there shows your mean. So the mean of that distributions means if you are going to pick one value that you are going to tell the press, that would be your best sort of guess if you like. And you can see the uncertainties.

Here we say somewhere between, say, 11 and 29 people with --- percent confident. It was within that range. And then over here I have got bloody diarrhea. And we have got distribution of uncertainty, somewhere again between, say, 700 and a bit less than 2,500.

(Slide.)

And finally, I have got non-bloody diarrhea -- bloody diarrhea in the first one and non-bloody diarrhea enteric illness. And we have got somewhere between, say, 2,000 and 6,500 people.

(Slide.)

And if you add those all together, the total number of people with invasive, bloody and non-bloody enteric infections, then we get a total somewhere between, say, 2,000 and 8,000 people a year in 1998 who would have been to the doctor, prescribed fluoroquinolone, but to whom it was of no benefit.

And I suppose you should compare that with, say, the two and bit million of people who have Campylobacteriosis. And so we've got 4,000 out of two million. That is a cumulative distribution, again, saying that it is somewhere between, say, two and a bit thousand and a bit more than 8,000.

(Slide.)

So in Section 4, I was interested in looking at the contaminated chicken because I want to compare humans and the contaminated chicken populations. And this is a very simple analysis. I simply looked at the prevalence of Campylobacter in chicken carcasses at the end of the sorting process. And that is a point estimate -- sorry, that is a point in the process in which we are measuring.

If we had measured at the beginning of the process, we would have a different estimate of prevalence. So if you measured them at the slaughterhouses that they came in the slaughterhouse, you would have a different measure.

And for the purposes of this risk assessment, it is not really so relevant where we measure except it would be nice to measure as close as we can toward the consumer. So the first, so long as we can go towards the consumer. And this happens to be a good place because at the end of the chiller, they are then going to go off into a whole bunch of different paths that we can't monitor so easily.

So I took the prevalence of Campylobacter in chicken carcasses which is based on -- well, we have data on that and, again, the prevalence of fluoroquinolone-resistant Campylobacter among Campylobacter isolates. And so if you multiplied those two together, you get a good estimate of the prevalence of fluoroquinolone-resistant Campylobacter carcasses.

And from data, we have data on the consumption of the boneless, domestically-reared chickens in the U.S. in pounds. And so the volume of chicken consumed is the average per person multiplied by the population. And then we look at the total quantity of boneless, domestically-reared chicken contaminated with fluoroquinolone-resistant Campylobacter in the U.S. And that is just simply the total volume consumed multiplied by that Campylobacter-resistant prevalence.

(Slide.)

And this is the estimate we came up with. It says that there is somewhere between 1 X 10^9. That would be 1,000 million pounds and, say, 2 X 10^9, 2,000 million pounds worth of Campylobacter-resistant fluoroquinolone -- fluoroquinolone-resistant Campylobacter contaminated chicken pounds.

(Slide.)

Okay. Section 5 is trying to make a connection between the contaminated chicken that is consumed and the human health impact. We take this expected incidence which I have called in my model $N3_T$. It is the total number of people would have had some human health impact out of the resistance from Campylobacter.

And we say that it is proportion to the poultry product -- poultry production V_i. And so there I have this constant of proportionality, K. And because $N3_T$ and V_i are very uncertain, we will have a lot of uncertainty about K.

It turns out that this works quite nicely under certain fairly minimal conditions because of something called a conditional probability identity.

(Slide.)

Okay. Now, how can we use this value of K, if you like, to make predictions about the future? Well, what we do is we say imagine V_n is a future annual volume of fluoroquinolone-resistant Campylobacter contaminated chicken that has been consumed. And we can work out what count that would be by monitoring the amount of chicken that is consumed and monitoring the prevalence of Campylobacter amongst chicken isolates and by monitoring the prevalence of fluoroquinolone resistance amongst those Campylobacter isolates.

So if we can keep monitoring this and have a good idea of maybe those trends, we don't even need to know very well what those trends will be. If we monitored them fairly consistently, we don't have to model the trends. We can just simply see where we are at any one point.

And we can use this very simple equation here which would tell you the number of new human infections.

And that is going to be a Poisson distribution where the N here is this new amount of contaminated chicken, and divide it by K.

So at any stage, we can start to talk about the risk that actually is out there by having this prevalence of fluoroquinolone-resistant Campylobacter.

(Slide.)

Now, this model does assume that the value of K remains constant. In other words, that human behavior remains constant. But I would say particularly with respect to things like behavior in the kitchen.

Now, we had a previous speaker talking about they didn't think that most of the contamination, most of the illness came from directly consuming poorly cooked chicken, but from poor handling practices. Now, we also had Doug Powell stand up and say you can't educate people. And I suspect it is going to take quite some time before you really will start people to handling the food a bit more properly.

I had fun yesterday coming back on the plane. We were -- Louise and I -- she is from England, as well. We were sitting on the bus. And the bus is taking us out from the airport to our car. And it is say, "Don't forget to put your seatbelt on." So at least you, too, try and teach your people. We don't do that at all. We think it is funny.

(Laughter.)

You remember how English have quirky sense of humors. That is us. So it tells us human behavior remains constant. It also assumes that the resistant pathogen retains the same level of pathogenicity. And it also perhaps more so -- a more difficult assessment is that it assumes that the microbial load in a contaminated portion remains constant.

Now, if, for example, you were to introduce irradiation as a process, then that would -- this assumption would fall down. Mind you, at the same time, you probably wouldn't have the risk anymore. So that wouldn't be such a bad thing.

(Slide.)

Okay. Now, if we quantify -- how do you quantify the human health risk per year? And this is really a large part of why we are all here. It is a policies decision. But in order to present the results of my risk assessment, I have presented four different things here.

I have talked about -- if you remember those -- the total number of people who were actually affected because they had -- they consumed that domestically-reared chicken, they went to the doctor because they got Campylobacteriosis. The doctor said, "Here, have some fluoroquinolone. You will be fine." And they weren't.

Well -- and there is a bit of argument about what that would represent, perhaps an extra two days of illness, who knows. Anyway, what risk does that represent? It depends who you are. If you are just your average person in the U.S. population, then we can say the risk is if you like the actual number, the average number of people who would be -- in a year who would be affected in that way divided by the total population.

So the denominator is the U.S. population here. And for those people, for the likes of you and I who hopefully are not sitting here with Campylobacteriosis thinking about going to the doctor this afternoon, well, then the probability is maybe one in 61,000 or so. That is an expected value. There is uncertainty around that.

Or if you want to look in terms of probabilities, it is 0.0019 percent. And for most of you, you are not going to say, oh, 0.0019 percent. It doesn't mean a lot. But maybe one in 60,000 means something more to you.

(Slide.)

Now, if you were sitting here with Campylobacteriosis, then the risk to you is something more like one in 521. On the other hand, if you had definitely decided that you were going to see the doctor this afternoon and you had Campylobacteriosis from the domestically consumed chicken, then it is going to be something like one in 63 versus if you actually went there and the doctor said, "Yes, you are ill", and he decided to administer -- or prescribe an antibiotic. That risk increases to one in 32.

(Slide.)

Okay. So I have got a number of uncertainty distributions about that. Here we have the one in X kind of format where we have the U.S. citizen. I just want to show you what I mean by there is still some uncertainty about it. So we have a considerate amount of uncertainty around those values I am giving you.

(Slide.)

Okay. Now, we need to analyze the uncertainty. We can use spider plots which are a nice little technique to determine where those key uncertainties are. If we know where they are, we know where we can take some more information.

And if we look at this analysis I will show you in a second, it shows that we -- in my view, we still have comparatively little knowledge of human health cases which is a very strong argument for increasing your FoodNet survey. I think -- well, if it were not for this FoodNet survey data, we would never have gotten started. And if it had wider coverage, we would certainly have a much better estimate of the human health impact.

(Slide.)

Okay. So, well, what on earth is this? This is a spider plot. And here I have got all of the key uncertain parameters associated with estimating the total number of Campylobacteriosis cases in the United States in 1998.

And the vertical axis here represents if we were to know that each one of those parameters was at its actual five percentile or its 20 percentile or its 50 percentile, these are places along the distribution of the uncertainty. We have about what that true value is.

If we would be able to say, now, we know what that value is, if it turns out that it was at its fifth percentile, then our estimate, the mean estimate of $N3_T$ here would be at that value. So if I take this little black dot one and it was at ninety-fifth percentile, well, then it would be this value.

In other words, this vertical range here represents in sensible terms, terms we can understand, the effect of actually really knowing what that value is. For some of those where they -- the flatter, well, really knowing the value doesn't make any value to our analysis.

In other words, our analysis is relatively insensitive to what that value might be or, in other words, what it really means is that we have sufficient data about those particular components and we should be concentrating our efforts in understanding other parts.

Well, the three bits from the point of view of estimating this total number of Campylobacteriosis cases, the three parts are the expected observed enteric infections in FoodNet data. More FoodNet data would be marvelous.

Also, in here, the second most important was the probability that a specimen, a stool specimen tests positive. And there may be some amount of controversy about that.

We certainly had to use -- the one point where we used data that didn't direct apply to the U.S. population. It came from New Zealand data. But our choice was either to assume it was 100 percent or to use some data. And it was the only data that I know of that was available to us. So as people have said before, if any of you out there have information for us, it would certainly help us improve our estimates.

And here we have the probability that the stool requested and submitted for non-bloody. So what is the probability that if a person goes to the doctor that the doctor will say, "Oh, you better give me a stool specimen." And we have a lot of uncertainty about that.

(Slide.)

In terms of the volume of contaminated chicken, well, we -- essentially it is the fluoroquinolone-resistant prevalence in poultry which is no surprise that we really have our most uncertainty about. But the really interesting thing is then to compare the ratio of $N3_T$ to -- divided by V_i. And that gives us -- from the point of view of the whole assessment, it tells us where we really need to concentrate on uncertainties.

And you see here, the PRC, which is that variable or parameter that is marked, is the only poultry-related parameter. So, essentially, it is the human health side that is really contributing the greatest amount to our inability to predict what the future holds.

(Slide.)

So if I look at the total amount of uncertainty, you can see where this is -- the quotient of $N3_T/V_i$ is what I am interested in. And you can see that if I wrap up all the uncertainties of one versus the other, this is the human health. And human health has a great deal more uncertainty, in other words, has a much larger vertical axis range than the chickens.

(Slide.)

So in conclusion, because I have got my stop light here, in conclusion, the modeling approach is simple. And simple will annoy some people. But it will also make an awful lot of other people very relieved.

It is simple -- I would like to think it is very transparent. And it makes few assumptions. I hope that we have done a good job of being quite explicit about what those assumptions are.

It is fairly easily updatable. And, therefore, if you choose to use it, it can remain very current. And a very key part of this is it recognizes uncertainty. And, of course, as I have said a couple of times already, our uncertainty would improve a great deal if we were to be able to collect more data.

And I believe that the model can be used as an aid to regulatory decision-making. And you will notice that I have written down "aid to." And as we have had our speakers say before, it isn't -- numbers are not the only thing. You have to look at a lot of other input parameters into a decision. So I in no way believe that this is the conclusion to your decision-making. Thank you very much.

(Applause.)

DR. BEAULIEU: Questions?

DR. KASOFF: Mark Kasoff from London. I found it a very interesting talk. I have trouble with one step which is where the patient was acquiring the organism, has symptoms and has required a resistant organism is given the drug because we know that the great majority of these patients don't need any antibiotics.

How did you estimate the extra morbidity because he is taking the drug against the resistant organism? What estimate did you put in for that? Because in the end, maybe --- for the overall damage to the society of this resistant organism.

DR. VOSE: You have a good question. And certainly, we did look at the effects of the extra morbidity. We have very varying data, very widely varying data and not a great deal of consensus about I think what that true value is. But roughly speaking, it turns out to be I think about two extra days of illness for the vast majority.

I didn't include it because essentially it becomes a constant parameter. You multiply the number of people by the number of extra days of illness. And so I have left it at just the number of people.

But if you wish to convert that for yourselves into the human health impact in terms of morbidity, multiply it by two and call that days -- personal days of illness. And I think you have got a reasonable estimate. I wouldn't hang my hat on it, but it would be reasonable.

DR. BEAULIEU: Yes?

(Away from microphone.)

MR.   : The model --- statistical uncertainty ---.

DR. VOSE: I agree with you. And the mathematics, of course, can only describe the statistical uncertainty.

But Kathy Hollinger and Mary Bartholomew -- I hope I don't put you on the hot spot for saying this -- but they are going to describe the biological assumptions and uncertainties in their presentation this afternoon. So perhaps better to address that question to them.

(Away from microphone.)

MR. : Mr. Vose, my --- 61,000 ---.

DR. VOSE: Well, the bottom line, let me just drive up here. You can say -- I think the bottom line depends on what you want to say, you know. I mean, I am sure that if you are -- well, you can be on different sides of a particular fence here.

So I am not going to give you a bottom line figure. It really -- I think what I tried to do is by very explicitly talking about uncertainty, I let you decide what you mean by a level of risk.

And I think it is quite -- I think that is very appropriate because if you are on the side of human health, then obviously you would like to try -- you would see any human health impact as being awful for you and you would take it -- one would say -- some would say an alarmist's view.

But you would take a conservative view about that assessment versus if you were some other person, you might take a completely different view. So you choose what value you want to make out of those distributions. I am not going to give you that. That is not a cop-out, I promise.

MR. : I think one thing that is useful to consider is that although mention of the model, but wasn't shown in your presentation, is to try to understand the population of people from whom these people with potential harm are arising.

And if the model predicts two million people with Campylobacter infections and the data demonstrates that seven percent of those people have a fluoroquinolone-resistant infection and the resistance is a consequence of fluoroquinolone use in poultry, there are about 140,000 people a year who have a fluoroquinolone-resistant infection. And the resistance is a consequence of using fluoroquinolone in poultry.

That is the population from whom we tried to decide what the harm might be. And the model shows that there are about 5,000 people from that 140,000 that are affected that you modeled.

Those are the people who are sick enough to seek care and the physicians concerned enough to get a culture and also concerned enough to prescribe fluoroquinolone. And so we would say that those are -- that it isn't appropriate to look at those numbers.

But also you should consider that amongst those

5,000 people, there are about 20 the model predicts that have a bloodstream infection, an invasive infection. And it would be a simplification to judge that those people with a bloodstream infection would just suffer two additional days of illness that might be more severe consequences for them. And we would judge them to be severely harmed by this.

We do agree that the moderately harmed people do equal about whatever the 5,000 minus 20 is. Those are the moderately harmed people, people with two additional days of diarrhea.

There are also people that are mildly harmed that are not in the model. And those people that are mildly harmed are people that are ill enough to seek care, are -- but the physician does not prescribe antibiotics.

And there is increasing data or at least we have preliminary data that demonstrates that people with a fluoroquinolone-resistant infection, even if they don't -- aren't given antibiotics, have a longer duration of illness.

So that needs to be more fully explored. But there is potential harm to people, even to those who aren't prescribed antibiotics. Then we have -- I mentioned there were 140,000 people in the model.

DR. VOSE: At least, yes.

MR.   : And we just described the 5,000 people that were severely and moderately affected and the

10,000 people that are mildly affected, if you follow my logic. That leaves 125,000 people who are ill, but do not seek care and do not get cultured. And because they don't get cultured, we can't break them into groups of who is resistant and who is susceptible.

So it is very difficult to study those people to see if there is a difference in illness between those two groups. So there is this very large uncertainty, a group of people that the harm is uncertain but is theoretically possible.

And so I just wanted to point out the misstatement about the two days of diarrhea is not the only harm that your model portrays.

DR. VOSE: Okay. If I can reply to that, I entirely agree with you, Fred. And it was an approximation to say two days. But the reason I did it is because if we look at, say, the bloodstream infections. Perhaps there is an extra eight days. We had no data at all about the extra illness there would be -- that that would equate to.

But I took the approach that we are talking about 5,000 people versus 30 and the 5,000 times two days versus 30 times eight. It was a second order effect to include the extra days of human health effect.

But I agree with you. I thought it was better really to present the three sub-population as they were rather than aggregate them from the point of view of human health days because it felt to me that we were making more of an assumption that we haven't really needed to do.

Now, I also -- I think you have a point about the denominator that you want to talk about. But although that is one point of view, we spent a great deal of view discussing what that denominator should be in terms of estimating the risk to human population.

You say it is the number of people who actually have a Campylobacter infection that is fluoroquinolone-resistant. Now, perhaps that is the right one. But also, if the person never seeks care, does it really make any difference whether it was one strain of Campylobacter or another? If there was no difference between the human health impact on them, I would maybe argue that it wasn't relevant. But I am afraid -- yes.

MR. : But the point is just because they don't seek care and we don't have data where there is a difference in severity of illness does not equate to no difference in severity of illness. That is an assumption that should be explicit that, in fact, there is biological reason to believe that there would be a difference in severity of illness.

DR. VOSE: Yes, okay. And there was some data that -- we certainly explored that, whether there was any difference between the level of illness that somebody had if they had fluoroquinolone-resistant Campylobacter or non-resistant. I don't know whether Kathy is going to talk about that. But we took a judgement call. And I hope we are explicit about it in our report.

We assumed that there was not. But if there is data that says that there is, then obviously we would have to address it. I totally agree with you.

MR. : Yes, I would like to come back to a comment that Tom Shryock made a while ago regarding the numerator and not the denominator. The FoodNet data shows a three-time increase case load of Campylobacter and even larger than that with Salmonella in infants less than a year of age.

Now, we recognize that infants don't eat chicken, raw chicken particularly. And it is probably unlikely many of those cases even arose from contaminated chicken juices, although some could have. That clearly is a possibility.

Not knowing where those cases came from, it seems to me that when you get on down in your calculations in estimating the number of cases that come from chicken consumption, we must adjust for that because clearly those numbers cannot be related to chicken consumers. If you look at the data, the case load is something like 55 per 100,000 in infants less than a year of age and it drops dramatically to 20 after a year of age.

So there seems to be adjustment that would be needed in the data, in the modeling when you go from the estimated cases to those that are related to chicken which seems to me would reduce the numerator quite a bit when you get down to those cases of chicken. So I would suggest that that data needs to be re-examined.

DR. VOSE: Thank you. Well, I have to say that a very big difficulty we had in doing this risk assessment is to determine the proportion of people for whom the Campylobacteriosis really originated from chicken. And that is an incredibly difficult assessment to make.

And I think that some of that falls into what you are talking about because we don't have -- we can't -- if somebody comes to the doctor and they say, well -- you work out they've got Campylobacteriosis, how to work out where they got it from.

By the time that they've got it and it has been three or four days, and goodness knows whether you eat chicken and beef and play with cat and dog and any number of things. So if there is information in there that would let us be more specific about who really are getting it from chicken, that would be great.

And just to remind you that one of the previous speakers was talking about that they didn't think it directly comes from chicken, but from handling of chicken was in a large number of cases. Now, isn't that difficult to work out, how many people really got it from chicken when it comes from handling. Certainly not by looking at the amount of foods that they cooked.

MR. : I spent a number of years in pediatric practice and I actually don't have any problem understanding how infants under 12 months of age would acquire food-borne infections. They spend a lot of time in the kitchen along with mom while she is preparing the food. They receive solid food much earlier than us pediatricians recommend.

We, you know, tend to recommend formula only until six months. And that is the exception in my experience in pediatric practice; that they very often at their six-week check-up, you find that mothers are giving them solid food because they think it helps them sleep better through the night or something like that.

But the point I am making is that, you know, infants -- the definition of infant is less than 12 months. By the time they are 12 months old, they are pretty mobile. They spend a lot of time in the kitchen. I just don't have any problem understanding it.

(Away from microphone.)

MS. : --- breast milk --- the mother is

constantly handling the baby ---.

DR. BEAULIEU: We will have to limit our questions to those folks who are at the mike now in the interest of time.

MR. : Two sort of technical comments about that problem. The first is that even though the incidence may be higher in people under a year of age, there are a lot fewer people under a year of age than there are in all the other age groups. So a high incidence doesn't mean a high fraction of cases.

The second is that there are three studies in the report from which the proportion due to chicken consumption were estimated. One of those uses students. So that is not a representative sample. The other two are population-based and, therefore, should take into account that age distribution.

DR. VOSE: Thank you.

MR. : I have a question. It goes to the front end of the cycle, not the back end of the cycle. Apparently, there is a 17 or 18 percent incidence of Campylobacter-resistant fluoroquinolone -- fluoroquinolone-resistant Campylobacter on poultry. And I have read through the document. And I wanted to listen here to see what you said.

And you touched very briefly at the start of your presentation about one shed of chickens receiving the fluoroquinolone and all the chickens in that shed receiving fluoroquinolone. And I don't question that, although in this country we call them houses. But that part doesn't make any difference.

But my question is the -- and there has been studies done on this that show that approximately one percent of the chickens grown in the United States are treated with fluoroquinolone. That is pretty low. Let's just say that it is even two, three, four, five percent. I am curious, in the development of this model, how have you accounted for that?

Because, you know, I don't question that the usage of the drug will lead to some resistance. I don't question that part. But I also question that there is other mechanisms for development of resistance. And I didn't hear anything in here that accounts for the very low usage of fluoroquinolones in chickens.

DR. VOSE: Okay. You have a very interesting point. And, okay, you have a different way of housing your chickens than -- rearing your chickens than I am used to. You have deep litter processes here. So there could be a connection from one --

MR. : What do you mean by deep litter?

DR. VOSE: Deep litter, isn't that what -- where you re-use the litter?

MR.   : There are areas of the country that re-use litter. There are areas of the country that do not.

DR. VOSE: Do not, okay. Absolutely. All right. So there is a potential mechanism even though you may -- you treat a chicken from the past, another chicken can get it at a later time though it has never directly received fluoroquinolone itself. But -- and there are a number of -- there are all sorts of different things that can happen.

For example, at the plant, there could be cross-contamination galore at the plant, particularly in the chiller and in -- I know the thing that takes off the feathers, the machine that eviscerates the poor thing. And, you know, I have been there. I have a diary where I was taking notes. And I have this page -- this double page splattered with blood. I will never forget that.

But they have this thing that goes whoosh and removes the whole of the inside, you know, the poultry carcass in one hit. It is quite an impressive piece. But it goes round and eight times later, it is doing the next one. There are all sorts of different things, although I know that certainly the slaughterhouse that I went to was an incredibly clean place.

And certainly, the industry -- and I have to say that this is not in the United States, though I am sure that you have some of the practices -- but the industry took enormous pains to try to reduce the amount of cross-contamination.

I don't pretend to know exactly where that -- what levels of mechanisms of cross-contamination occur. And I think that that is one of the real difficulties of doing the farm-to-fork risk assessment, is being able to quantify all those levels.

So what I have tried to do is say, look, I don't know how they got all fluoroquinolone-resistant Campylobacter on that chicken. I admit that I presume that the fluoroquinolone resistance comes from administering at some point to some chicken fluoroquinolone. And we can certainly argue about that.

But having made those assumptions, at this point here, out of the chiller comes this chicken. It is contaminated or it is not. And I don't know how it really got there. But that is the thing that is going out to the consumer. Okay.

MR.   : I really don't question that part of it. But what I am saying is I think somewhere in here, you should try to separate the resistance from the usage of the drug. I am not saying drug usage leads to resistance. But there are other things that lead to it, also. And let me just raise a point -- and I know people want to go to lunch.

But there is a point, we had checked broiler houses where we have moved chickens and just gone in on built-up litter and have done what we have done a wash-down which is cleaning and sanitation. And we could find Campylobacter in that house before we went through this process. But we could not find it after we went through that process.

And I am not saying we get them 100 percent all the time. All I wanted to get you to do was to think about the fact that there could be something else involved in this whole mechanism besides using fluoroquinolone. That's all.

DR. VOSE: Okay. Thank you. If I can just make a final comment to you. It would seem to me very worthwhile if the industry, the poultry industry was to -- and it sounds like you are doing it right now -- but was to try to do a risk assessment to identify where that contamination comes from. Now -- and that's -- I don't say that that is not a big job. I think it would be a big job.

MR.   : No, no. It is.

DR. VOSE: But you would have some clue as to where it came from and the ways that we can change the use of fluoroquinolone -- or one can change the use of fluoroquinolone to minimize the resistance in poultry at the end of the process.

MR. : Those, in fact, are things that we have been doing. We don't have them all because there is a lot of these questions we don't know the answers to either. And one of the things is the chicken industry that we are working on is guideline manuals for use of products that we use to minimize the kinds of problems that you are talking about.

But you are right. I think you see it the way I do. This thing is more complex than what it appears.

DR. VOSE: Thank you very much.

MR. : Thank you.

MR. : I am from the Canadian Food Inspection Agency. I would like to weigh-in on both sides of the developing camps here. On the one, we have done a quantitative risk assessment for Campylobacter jejuni in fresh poultry in collaboration with Norm Stern at ARS, Russell Research Center in Athens, Georgia.

In our model, we actually did take a stab at modeling the cross-contamination impact in the kitchen as well as the preparation and consumption of cooked poultry. And in the manner that we modeled it, we came up with final estimation of risk approximately 200 times the risk of the cross-contamination in dripped fluids on counters, etcetera, being approximately 200 times that at consuming prepared and cooked chicken.

Now, there is a huge amount of uncertainty in that. There is a great need for further investigation and further work. So I don't -- but I don't -- from that, I don't have any difficulty in sort of buying into that theory or hypothesis about cross-contamination having a very important role.

On the other side, like the gentleman before me, you said initially, David, that one unique thing about getting into developing this model was that you had data for all the points along the way. And that is always an important concern in developing process risk models, quantitative risk assessments.

But I am not hearing that you really have data on that front-end association saying that the -- that very large assumption saying that the fluoroquinolone resistance in that ---

(Audio missing due to technical malfunction.)

DR. VOSE: --- it sounds logical if you take your chicken and it lives its life in the shed or house, whatever you call it. And then it goes from there to the poultry slaughter plant and it hasn't really been anywhere else. Then I guess to me it strikes me as a reasonable assumption.

But certainly if there was any data that would say otherwise, then, of course, we would be delighted to look at it.

MR.   : I don't disagree that it seems somewhat reasonable. It's just that the question is we don't really have the data.

DR. VOSE: No, there is no causal link.

MR.   : Yes.

DR. VOSE: Yes. And I don't think this risk assessment has ever set out to prove causal links. If you have a criticism in that regard, I think it is reasonably unfounded. In any microbial risk assessment, there is never an attempt to make the causal link, just to look at the quantitative implications under a certain set of assumptions.

So we -- in microbial risk assessment, we make assumptions. And scientists find the causal links to either back us up or tell us we are wrong.

DR. BEAULIEU: Last comment.

MS.   : I just wanted to say that a risk assessment question given to us by our risk managers really did not have that question or that issue within the scope of the question. We were to look at what is the impact of fluoroquinolone resistance from -- in humans from exposure to chicken.

So we really didn't address the drug use issue at all in this risk assessment. There was no attempt made. So

I would like to say that, you know, that is part of the reason why this really isn't in this risk assessment. It would probably more be part of, you know, the risk management decision to use this risk assessment question that we needed to address.

(Away from microphone.)

MR. : It just seems that critical ---.

MS. : Yes, I think that we have seen that -- you know, evidence coming out of other countries or we have seen clinical trials. And we have seen resistance develop in relation to use in both humans and animals and in laboratories when you use it in bench top tests to create nalidixic acid resistance, for example, in microbes to mark them for further studies. So you see it, you know, developing fairly readily in response to exposure to the drug. And it is a characteristic of that class of drugs.

DR. BEAULIEU: Thanks. Thank you.

DR. VOSE: Thank you.

DR. BEAULIEU: We are running significantly behind schedule. You might have noticed. I am going to try to get at least -- let Tony Cox speak this morning. We may have to -- I will talk to Steve and see what he wants to do about his presentation.

Our next speaker at any rate is Tony Cox. He is President of Cox Associations, an independent Denver-based applied research training and consulting company that specializes in health safety and environmental risk analysis. He holds advance degrees in risk analysis and operations research from MIT. And he has lectured widely on topics in risk analysis, applied mathematics and computer science. Dr. Cox.

MATHEMATICAL VALIDITY OF THE CVM RISK ASSESSMENT

Dr. Tony Cox

DR. COX: Thank you. I am pleased and surprised to discover that I am the lunchtime speaker.

(Laughter.)

(Slide.)

Whenever you see a model with several dozen input parameters, you are entitled to wonder does the whole thing hand together; do the outputs fall from the inputs; is this thing valid. And I guess I could get us to lunch pretty quickly by saying yes and stepping down.

I thought I should give a little bit more detail. But I will move quickly. To say has the model been validated or to address the mathematical validity of the model is going to come down to two things: Is it sound meaning that the calculations are correct? And is it -- given its assumptions. And is it useful, meaning that the assumptions are ones that we can live with?

And you will notice that the big assumption is that the incidence of bad outcomes that we don't want is proportional to the volume of outgoing chicken. I mean, K is the key assumption. And then there are a lot of little assumptions.

And so I want to spend the next few minutes, fewer than ten, fewer than eight, the next few minutes just looking at the key assumptions and then saying why I think that this is a pretty good approach. It is a pretty sensible study. It does hang together.

It has to make a few baroque assumptions to get across big data gaps. But it is very explicit about that. So all in all, I think it is a job well done. I want to invite you to critically examine a few assumptions and see if you share that conclusion.

The strength of the model is its listing of all the parameters, most of the assumptions and the key uncertainties about those things. So that anyone of us can reproduce at least the calculations. That, of course, is attractive.

(Slide.)

Among the explicitly listed assumptions are things like attribution of fluoroquinolone resistance to chicken, stability of risk estimates over time and across populations, assumptions about care-seeking behavior. Of course, these are areas where there is a lot of uncertainty.

There is probably a lot of variability.

But the narrow validation question is due to conclusions follows the premises, do the assumptions correctly propagate through to give risk values, within that narrow context, we can make any sort of assumptions we want and just say, well, is the calculation accurate. And the calculation should be pretty accurate. I will come back to that to suggest how we can quantify the accuracy.

But it is also I think fair to say a model is more than a set of assumptions and a set of conclusions. What it is a way of calculating outputs, calculating conclusions from inputs. So if you don't like the assumptions, change them. I mean, that is why it is a model instead of just a statement of what someone believes to be true.

But in addition to the explicit assumptions which I think are well handled, there are some implicit assumptions. By the way, I think those are pretty appropriately handled, too. But I want to pull some of those out.

(Slide.)

And in the interest of hunger, I am going to focus on just the ones of these that are most interesting. Those are independent. One assumption made throughout is that we can take a lot of input parameters and treat them as if they are statistically independent.

So I want to say a few words about that. I think extrapolation between populations we are going to pretty much skip over. It is obviously important. There is always room for refinement. But I think that beyond saying those things, there is a bunch of technical details. Right now, the truth is we don't know how well the FoodNet population represents the larger U.S. population.

I myself having grown up in Virginia think, you know, people who live in the south eat more chicken. So to what extent is the geographic balance there? The answer we don't know. So let's acknowledge that uncertainty and say it is worth looking at in more detail eventually and move on. You are using a simple ratio which is probably an appropriate starting place.

Similarly, for folks who are interested in modeling, there is a lot of interesting stuff to be said about aggregation of end sequences. Something that I see as a very strong part of this model is the calculation of one big probability by careful examination and eduction of data from a whole bunch of little probabilities that multiply into it.

We could talk, and it would be fun if you are interested in modeling, about, well, do you do better by estimating the whole, big probability. I am talking here about the product of what's the likelihood that you get sick, that you go to see a doctor, that he prescribes a drug, that your tests are positive and so forth.

There is a statistical issue which is do you better by trying to model the product of all those things or by trying to model each piece and then multiplying them together or by doing both and realizing that you need to get the same answer whichever way you do it. And those are interesting technical details.

You might be able to slightly reduce your uncertainty about the results if you exploit the fact that there is more than one way to calculate the same answer. There. Now, that is a little abstract of stuff that we could talk about under aggregation of event sequences. But I plan to skip it because I don't think it makes much difference in this analysis.

And, finally, I will say a little bit about modeling of input uncertainties and suggest some things that might be done to further boost the comfort in this model which I think starts pretty high. Okay.

(Slide.)

So the independent assumption I do think is worth noting. And the question here is should input be modeled as statistically independent which is how they are modeled right now. For example, the probabilities of care-seeking behavior among those with bloody and non-bloody diarrhea, are both models -- each separately as being models drawn from some appropriate gamma distribution.

My question would be if you learned that one of those is much higher than expected, suddenly people are all hypochondriacs and they are rushing to the doctors, you know, immediately, might that affect your beliefs about the other of these two parameters. Is it only people with bloody diarrhea who are hypochondriacs? I mean, I wouldn't blame them.

(Laughter.)

But if it is a social phenomenon, being surprised on one might indicate that you might be surprised on the other. So all the formulas in the model can be generalized immediately by conditioning each component of the product, all the things that have preceded it.

And I will simply note that that is one area for exploration which we could look more carefully at possible dependencies among inputs. The expected impact of that generalization is small provided that independence is a reasonable approximation. And now suddenly I am talking about the real world, what is going on physically. Is this a reasonable approximation? And I don't know the answer to that.

So I will say mathematically it would make sense to allow for the study of dependencies among inputs. I am inclined to think that it wouldn't change the answer a whole lot. But I don't know that for a fact.

(Slide.)

Okay. Extrapolation, I promised you I would skip over this. So I will. Aggregation of events, I already spent more time introducing it than I had intended to spend talking about. So I am going to skip past that.

(Slide.)

Modeling input uncertainties, the middle point that uncertainty is about joint distributions and dependence among uncertainties to be analyzed further, I would make that the recommendation.

If it turns out that the community generally for political or other reasons wants to push on this analysis, this initial analysis and say we have got to be more comfortable before accepting the calculation of outputs that comes from inputs, then I think that making these I suspect minor refinements would be worthwhile.

In the same vein, there are a number of technical options for estimating joint distributions of inputs including the Bayesian approach that David has taken and including the frequentist approach which looks an awful like it.

There are other approaches that could be explored. And if one wanted to push hard on building comfort in the input-output calculator, I would recommend looking at some additional technical approaches.

Again, probably the details aren't that important. But I will be delighted to share them with you after lunch.

(Slide.)

Okay. Model formula uncertainty is one of the biggest problems in most models with a few dozen input parameters, is that you are not only uncertain about the inputs that go into this thing, but you are very uncertain about the formulas for combining them.

An admirable attempt has been made in this piece of work to make all the formulas just logical identities. There is supposed to be no empirical dose response relations or anything that might be complicated.

Despite that fact, David said I might mention -- and, in fact, I am going to mention the fact that whenever you have even a ratio of uncertain quantities, you are to be quite careful of the ratio of means is not the mean of the ratios.

There may be biases, although they should be small, that arise from uncertainties about formulas and from the fact that there may be multiple numerators, multiple denominators that are getting munged together, munged being a technical term. The less technical term is mixture distribution.

In any case, there may be some slight biases there. I don't think they would invalidate the main conclusions of the model.

Okay. Now, let me wind up. There is a concept at the very end of this slide, simulation calibration. And let me share that with you because this is a recommendation for something else that should be done.

Oh, one more major point. All statistics and all mathematics aside, I hope that many of you notice that the spider diagrams show a range of uncertainty that is pretty darn small, typically a factor of two on the Y axis. Those of you who have been involved in other risk assessments might be used to a factor of 10^6 on the Y axis.

So from a certain standpoint, the sensitivity analyses to me build a lot of confidence in the range of results we are going to get out. And all this probablistic tweaking is a small refinement inside a really narrow range by risk analysis standards.

So here is the thing that I think would be a good idea and that I would urge for consideration as a possible extension of this work and not necessarily a very difficult one. If we take the whole model, it is a big calculator. Let's look at it as a black box right now. And we want to know, well, how biased, if at all, are the outputs that it gives, how trustworthy are the outputs that it gives.

One option for doing that is to drive this model, exercise it, using a front-end simulator that says, look, we are going to make up a -- an expected nominal number of cases. We are going to make up a true value.

Then we will simulate what random sampling from a large population might yield given that true value. Are you with me so far? We are going to simulate what is going on. We are going to simulate the sampling process.

Then, by gosh, we take that simulated data from the sampling process and run it exactly through the model just the way the model is right now. The model is a big black box. You put stuff in, you can get stuff out.

What you get out is the estimate of the true but unknown quantity. But wait a minute. The quantity is known in the simulation context. You start knowing the right answer. You drive it through the process. You see what the model says, compare it to the right answer which you knew going in. I recommend that that be done.

I expect that the calibration curve will look like a 45-degree line meaning -- or will be close to a 45-degree line. I would be surprised if it were spot on. But my point here is that we don't have to conjecture about whether the logic of the model is so well developed that we are sure we are going to get the right answer.

We can find out being much stupider about it, not trying to reason our way through it. Just say, well, here is the right answer, sample from it, exercise the model, do we recover the right answer. So I would recommend that. I love the sensitivity analyses. We could do more to things like sensitivity to population, heterogeneity.

Since I am a mathematician, I have no problem saying things like, well, if one person ate all the chicken that was produced, that would limit the number of cases you would see. All right?

(Laughter.)

In conclusion, model structuring calculations are well documented and logical. I think the model has good face validity. The model-based risk projections are credible in the sense that the logic isn't unsound given the assumptions, the conclusions I expect do follow.

Uncertainties in input quantities are explicitly and I think by and large appropriately modeled, although one can quibble about technical details. I recommend doing the calibration exercise that I have just mentioned. Thank you.

(Applause.)

DR. BEAULIEU: Thank you, Dr. Cox. We apologize for cramping your style which is considerably in any event. In the interest of appetites, we are going to --

DR. COX: Is it chicken for lunch?

(Laughter.)

DR. BEAULIEU: That's up to those folks out there having heard this morning's presentation. Are there, in fact, any questions from the mathematicians in the audience for Dr. Cox? One. David Vose.

(Away from microphone.)

DR. VOSE: Yes, one question. I would just say I think it is a great idea doing that calibration ---.

DR. BEAULIEU: Thanks, David. I have done a terrible job of keeping us on time this morning as you have noticed. I would try to get everybody back in here by 1:30. At that point, folks are going to be up here talking I would anticipate. So try to be back here by 1:30.

DR. SUNDLOF: I have one other announcement. I said earlier this morning that we would be out of here by 5:30 sharp. Since the last two presentations, I have done an uncertainty. And with 95 percent confidence now, we will finish somewhere between 5:00 and 6:00. Okay.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N   S E S S I O N

(1:40 p.m.)

CHALLENGES IN ASSESSING AND REGULATING THE RISK OF ANTIMICROBIAL USE

Dr. Stephen Sundlof

DR. SUNDLOF: In the interest of time, I think I am going to go ahead and start my talk. Most of -- fortunately, I am going to try and move through this fairly quickly. One of the reasons is that most of the things that I was going to say, others have said. And I am talking about challenges in assessing and regulating the risk of antimicrobial use.

(Slide.)

And I think just from the questions that have been raised this morning, people are pretty well in tune to some of the challenges that we face. First of all, risk assessment is something that I think the U.S. Government and the world government is beginning to embrace as a very useful process, a more precise process. It gives you better definition of the risk. It is a transparent process as you heard this morning. And it is being embraced I think on a worldwide basis.

(Slide.)

But having said that, there really to our knowledge is not a -- there doesn't have a good history in terms of how these have been applied in terms of regulatory situations in the past. So we are really breaking new ground here by looking at a risk assessment and then trying to see how that might fit into a regulatory scheme. All of the regulators are talking about it. Nobody has really done it yet. So it is brand new territory.

We learned that there is not very many microbiological risk assessment models out there. Maybe half a dozen talked about Salmonella enteritidis, E. coli and Listeria as being some examples of recent risk assessments and the pros and cons of those and where their short-falls were. So it is a brand new area. It has great promise. But we are not really sure how we are going to incorporate these into the regulatory process yet.

The President's Food Safety Initiative certainly speaks considerably to the issue of risk assessment and that in order to help protect the food supply, that we need to be doing a lot more in government with risk assessments. Again, interesting, we are not really sure where we are going to go with those. And so that is going to be one of the great challenges in the upcoming years, is how do we actually use those risk assessments.

And I think there is agreement that the issue of antibiotic resistance as it relates to animal agriculture is a growing concern on a worldwide basis and not just in the

United States. We are assuming that resistance develops from the use of antimicrobials, the transmission for the food-borne organisms that we are talking about, especially Salmonella and Campylobacter, are generally not from person to person and that the most likely source is from animals.

These are the assumptions that CVM is operating under at this time. And that certain antimicrobials are used empirically to treat patients that have developed food-borne bacterial infections. And so we have to consider all of those in the mix as to what is going to be the best public health policy.

(Slide.)

The model does assume that resistance is due to antimicrobial use in animals. That was one question that was raised this morning during David Vose's talk. And there is evidence, there is epidemiologic evidence that seems to point in that direction.

Obviously, any additional information that we can get will help us in determining whether or not that is the right approach. But presently I think that the weight of the scientific evidence clearly points to the use of these drugs in animals as the cause of the resistance.

Incremental health risk to consumers from compromised therapy is the harm, one of the harms that we are talking. We say incremental risk. And what we are talking about there is that people are already ill at the time. And then failure of treatment results in prolongation of their -- of the disease that they already have. And that is what we are considering as the incremental increase in risk.

And how do you model that? What is the best way to model that? In the model, only the risk from the use of fluoroquinolones in chickens is assessed. There are all kinds of other antibiotic microbials. There are several different diseases of importance that may be implicated if there is resistance from the use of these drugs in animal agriculture.

And we have a pretty good example of Campylobacter. We actually had some access to some good data. What about some of these other ones? Can we apply the same kind of approach to other ones?

I can say that the risk assessment model really did help us to focus on what the critical issues were. And it helped us understand better the scientific limits than if we hadn't done the risk assessment. So the risk assessment, and I can say from CVM's point of view, was a very much a belying experience. We think we benefitted greatly from it. It has changed I think substantially the way we think about assessing the harm that may be due to use of animal drugs.

The mathematical part of the model, as David Vose indicated, is simple and it can be updated. And even though we have a lot of uncertainty within the model even at this point, that additional information can help reduce those uncertainties so the model can be a living model. It can learn as we obtain more information.

But it also has its limitations. And you heard about many of those limitations today, especially where we need additional information and some of the assumptions have to be studied a little bit more carefully.

Well, what is CVM facing then based on the risk assessment model and dealing with the whole entire issue of antimicrobial resistance in food-producing animals? Well, first of all, we have to develop a quantitative definition of acceptable level of risk if we are going to use a quantitative risk assessment approach.

I think one of the speakers earlier this morning said -- I think it was Doug Powell said that we had gotten away from talking about zero risk. And I think that has been a very important movement for the United States and a lot of the other countries, as well. Nothing is risk-free. I think we will all agree to that.

But once you have said that, then it is important to ask the next question, well, then what is acceptable; what is an acceptable level of risk. Many of the international treaties, especially things like the WTO's phyto-sanitary agreement, talk about the concept of acceptable level of risk within sovereign nations. How do we define that? What is an acceptable level of risk. These are issues that we are going to be struggling with.

Determination of the human health impact, we talked about the assumptions that were made in the risk assessment model about that -- and the assumptions were made that there would be prolonged public harm simply because people did not benefit from the drugs that were administered.

Is that the correct assessment? Are there better ways of assessing the human health impact? Are there other end points that we haven't thought of that might be more sensitive, might be better indicators?

(Slide.)

The model can define -- you know, how do we define harm within the model? Is it just simply from resistant bacterial infections in people? Is it resistant infections in people that receive antibiotics?

Is it resistant infections in people that receive antibiotics and have an adverse effect that is measurable like prolonged illness or is it resistant infection and also those people receiving antibiotics that experience an adverse effect and for which there is no alternative drug treatment?

When we wrote the Framework Document, that last bullet there pretty much describes those drugs in Category 1 and drugs for which there are serious illnesses in people and for which there are no good alternative drugs. Those are the ones with the highest priority. So just defining what we mean by harm is going to be critically important in moving forward toward regulation.

(Slide.)

Okay. And then David Vose talked about this, but -- showed you this slide about depending upon what the denominator is, the risk is different. So you can have one in 61,000 if you consider the entire U.S. chicken-eating population. Your chances as a normal citizen of being affected if you eat chicken is one in 60,000, versus the population that develops Campylobacter, versus the population that develops Campylobacter and seeks medical attention.

And so we have to make a decision as an agency, what is the proper denominator. Traditionally, I can tell you that FDA has spread the risk over the entire population. When we talk about the risk of cancer, we are talking about a one in a million risk of cancer for all citizens.

Recently, with the EPA, they have the new law, the Food Quality and Protection Act which looks at sub-populations, looks at women and children. Are we moving in this area? These are public decisions, public health decisions, policy decisions that at some point we are going to have to come to grips with.

And so part of the reason for having this meeting is to try to get some of these concepts out on the table, have people thinking about them. And David showed you these and how you would map that risk. And it shows the uncertainty or the confidence with which those point estimates were made. So we will go through that quickly.

(Slide.)

And I will get to our conclusions then. So there is a clear difference. We are in a transitional stage in which we are shifting from risks that we traditionally have dealt with for chemical residues. And we are shifting to a different kind of risk which is antimicrobial resistance or just microbial contamination in general.

Very, very different. Very much more complicated. We are going to need all of the help that we can get in trying to get our hands around this issue.

The framework attempts to provide a mechanism to deal with this nontraditional risk. The risk assessment has helped us further along down that road. And we look forward to a lot of participation in helping us struggle with some of these very difficult issues. Thank you.

(Applause.)

SESSION 1: USE OF RISK ASSESSMENT TO EVALUATE HUMAN HEALTH IMPACT OF RESISTANT PATHOGENS

Chair: Dr. Wesley Long

DR. LONG: Okay. We are going to move right in to the afternoon speakers. First, we have Scott McEwen who is going to speak to us about using risk assessment to evaluate human health impact. And he is going to point out, of course, some of the things you saw this morning and re-emphasize some things and perhaps clarify some points that may not have been clear.

Dr. McEwen is a Professor at the Department of Population Medicine at Ontario Veterinary College, University of Guelph.

USING RISK ASSESSMENT TO EVALUATE THE HUMAN HEALTH IMPACT OF RESISTANT PATHOGENS

Dr. Scott McEwen

DR. McEWEN: Well, thanks very much, ladies and gentlemen. It is very good to be here. I was sitting down here reflecting as Steve was talking that I am kind of doubly disadvantaged. One is I have to follow his act on stage and the other is that it is right after lunch. And I remember as a young faculty member, the first post they gave me was teaching vet. public health. And the lectures were right after lunch.

(Slide.)

And I remember seeing a lot of yawning faces and people sleeping. And after one class, somebody came up to me afterwards and said, "Dr. McEwen, if it is my last hour on earth, I want it to be one of your lectures." And that really kind of boosted me up. I felt really terrific after that. And I went away and was thinking about how that could affect my pedagogic style and all that kind of thing. And I thought I better find out some more. So I went back and asked what exactly she was talking about. And she said, "Well, if it is my last hour on earth, I want it to seem as long as possible."

(Laughter.)

So I hope that is not the case with you. Well, this is not an easy talk to give after we have had so much excellent stuff on risk assessment already. But I have to say that I am really thrilled to be here. I think I kind of live for this stuff. As I say, I have been teaching vet. public health for years. And a lot of it seems kind of esoteric and hard to relate to.

(Slide.)

But in terms of the role of veterinarians and the things that they do and effects on public health, this is really cutting edge. This is as good as it gets in terms of a controversial issue that has real importance to society, real importance to us as professionals. And veterinary students just love it.

It is something that -- you know, for those of you who have been around for a while, you have seen it kind of all before. We get these shifts in opinion about what the impact is and how important it is. And I guess that is a natural sort of event.

As we learn more, we sort of engage in more discussion. We go back and forth. And really, as Steve mentioned, he talked about the risk assessment as a process. And I think that is an extremely important concept. That's the way I look at it. I look at it as a process.

And, yes, we can talk about risk assessment as a tool for helping policy and all that sort of thing. But I prefer to think of it in sort of a larger risk analysis context, that is, we are sort of looking for policy decisions, how to manage risk. We are using assessment to fortify that sort of thing. We are engaging right now in communication as part of that.

And I think all of the activities that the FDA has been involved and you folks in the United States on this issue is really an example of risk analysis, risk assessment and process.

(Slide.)

We can talk about policy. I am not a policy expert. I just kind of work at a vet. school. But there is a lot of kind generic things that come out about general principles for policy. You've got to focus resources on those things that really matter, those important questions, the primary issues.

We've got to try to make decisions, or at least policy-makers have to make decisions sometimes when the information is incomplete. And that can be very frustrating and especially when the consequences are not clear.

They also have to involve the greatest number of those who must be around to implement it. So they've got -- as I said before, this was driven home to me when I was in Berlin at the '97 meeting. And there the discussion was around risk assessment, risk management.

And I saw before my eyes this kind of notion that people that may not have felt totally franchised -- were unenfranchised I guess is the way of saying were -- created all kinds of problems. And it really drove home to me the notion that people have to be involved in the process if they are affected.

I have a quote by Henry Kissinger in his recent memoir. And he was talking about the principle for Presidents when they are deciding on foreign policy. But I think they are very much generic. They certainly apply to this risk assessment of drug use field, as well.

(Slide.)

I think one of the take-home messages that I would like to deliver is that there are really different types of risk assessment. The term gets used a lot of different ways. The one that we have seen today is one in its purest form, I guess. But there are a lot of other different varieties.

People sometimes talk about epidemiological studies, hypothesis testing and observation as a type of risk assessment. Really they are looking for evaluating risk factors, trying to identify risk factors of disease. And it is a form of analysis when we are looking at risk. But it is a kind of a different thing.

We will also talk about results of outbreak investigations and trace-back studies. Those types of studies where we attempt to identify through, as said here, molecular fingerprinting, but other ways of -- like clones of bacteria might come through the food system. And those are valuable -- provide valuable bits of information for risk assessments that support the kind of quantitative stuff we've talked about today.

These studies are often descriptive in nature. That doesn't sort of diminish their importance or their value. It is just a different way of looking at things, at different information.

We've got the -- what I would call the FDA study is a type of ecologic or population level scenario analysis. We are looking at the U.S. population, the total U.S. poultry production, that sort of thing. It is an ecologic study. It is kind of a separate type.

There is also, as David Vose referred to, a type of mechanistic or systems analysis, process risk model, the type that we are seeing evolving in the microbial field which is, again, a different approach. And I think some that we should see more of than we have in the past is more theoretical studies involving population biology, population genetics and that sort of thing.

But I guess the bottom line for all of this is the approach that we take very much depends on the questions that are being addressed and the purpose of the assessment. And that is something that has been stated already, but it can't be over stated.

(Slide.)

I guess in the past, we have seen a lot of sort of evidence or a lot of weight put on trace-back studies as a way of assessing the risk of antibiotic use in agriculture. And they still have an important role. And I guess I just need to fortify for you folks -- you probably don't need it -- that there is a lot of difficulties and challenges in that. But it still is a useful way of gathering information.

So, for example, treatment of cattle on farms. We are involved in some studies right now up in Canada with Doug Powell and Richard Reed Smith and some others trying to quantify and describe the types and extent of drug use that is going on in animal agriculture. So what kind of impact did that have on human health?

(Slide.)

Well, there is lots of difficulties in following, obviously, the treatment information through this system and the impact in terms of drug resistance through the system. Animals go to slaughter. They may go to auction marts, go to different farms. In all of those different locations, they encounter other strains of bacteria that may have acquired resistance elsewhere or they may supply them to different animals.

(Slide.)

Again, when they get to the packing plant, the slaughter plant in this particular beef example, again, we know that there are lots of changes that can be produced in the bacteria, both quantitatively and qualitatively. And we can introduction of new strains. We can have a growth of microorganisms and death due to various types of processes.

(Slide.)

So what do all these kind of changes and dynamics have in terms of the impact of human health which is the main sort of index that we are interested in? And, again, we have had looking through the literature a variety of studies that have evaluated this and have provided good information.

(Slide.)

Okay. What are some sort of broad applications to risk assessment in this domain of drug resistance from agriculture? I think something that hasn't been maybe emphasized enough is that there is a value here in pre-approval assessment. We have been focusing today in many places, we've focused on those drugs that are already out there in the market. And we have a resistance arising. And we are looking at the impact in that sense.

But now from a more sort of pragmatic purpose or theoretical basis, it would be great if we could attempt to anticipate the level of impact before drugs are actually approved. And there are difficulties in doing that, but there is also a lot of utility and possibly good value there.

(Slide.)

In other fields, if you are involved at all in food microbiology, you know that risk assessment, as Dave mentioned this morning, is being used extensively in trying to better develop food standards. What is the allowable level of microorganisms in food at the time of consumption?

The same thing for water microbiology.

We also can use them for hypothesis testing. What would happen if we do such and such? What are the effects of this intervention, for example, judicious use or prudent use in animal agriculture? What effects could that have on the level of resistance, the impact to public health.

And I don't think that we want to forget that another kind of application of these -- this approach is better understanding the biology of the process and better understanding leads to better decision-making as we said. And the thing that always gets left to the last and is hardest to do is trying to assess the economic and social impact.

(Slide.)

Well, you are not expected to actually read this at the back. I was sitting there before and I know how hard it is to see the screen. Basically, this is one of those slides that shows the complexity of the interrelationship among all of the environmental and other factors on resistance.

And I guess I put it up here just to underscore the kind of difficulty and sort of shock that one would get when you try to think about developing models that can capture all of these things at once. And so we really do have to make choices because of the incredible complexity of this system.

(Slide.)

And I think the choice the FDA has approached is a good one. It is similar I think conceptually to the -- to a risk assessment approach that was taken more than a decade ago by the National Academy of Sciences and, basically, again looking at the ecological impact of the sort of national level of resistance in animal agriculture and impact on human health.

We do have to remember that the ecological studies are very useful. But they also have some limitations. And some of this has been brought out this morning when we were talking about representativeness of samples.

(Slide.)

Basically, these types of studies -- epidemiologists refer to ecological studies is where the unit of observation is really the group. It could be a community or a national sort of level. The exposure, in this case, the exposure to drug-resistant bacteria I guess is -- and the disease are sort of measured at the group level. And there is lots of reasons for doing that.

But one of the problems is that you kind of lose a lot of information that applies to the units of that group. And it is impossible basically to control for any confounding that may be happening at that sort of level. So in some cases, it is a problem. But that doesn't mean that the studies have no value.

(Slide.)

I think we have to realize, again, that we do have a very hierarchical set of levels of organization and both in human society and in the way we have sort of managed farm animals. I could make this pyramid using a sort of farm structure. And it would have the national herd at the bottom, the states, sort of farm level, pens or different sights or pens and so on.

So we do have a very kind of hierarchical system which has major implications towards our sampling plans, for surveys. It has implications to dissemination of microorganisms. And it is very important eventually to try to capture these kinds of levels of organization if we are going to sort of better understand the process.

(Slide.)

I am not going to get into any kind of technical details about how risk assessments are being done in other fields. It is better left to the experts.

But I think it is important to understand in addition to the sort of ecological approach, there is this sort of mechanistic or process approach where we tried to follow the animal, the food product through the system of slaughter and processing, and try to measure or at least anticipate the effects that the interventions or the treatment effects or the heat treatment or the cross-contamination is going to have so that we get a better understanding of the quantity of bacteria that people are being exposed to I think at any given point.

And has been mentioned by Dave and others this morning, that we attempt to model what effects that quantity of exposure will have on human health that takes into account the variability in human population and all those factors to try to, again, characterize risk in some quantitative way.

(Slide.)

Okay. We'll skip that one. Now, in terms of just trying to schematically present the amount of information that we have, I think in a sort of rough way, highly unquantifiable sort of way, this is my impression. In terms of the four traditional categories of risk assessment, I would say that we have got proportionately a tremendous amount of information on the hazard identification step.

What are the nature of the microorganisms; the genetic basis of resistance; the ways that the resistance are transferred between microorganisms, that type of thing. And I think we need more of that. We have got a tremendous cadre of microbiologists and other biologists out there doing that kind of research.

But I think comparatively, we have very little information on the other steps in risk assessment, the exposure assessment phase and dose response and ultimately the characterization step. So what the implications are is that I think risk analysts concentrate on the exposure and dose response part of the equation for very good reasons.

But often people in other domains don't sort of recognize the importance for doing that. And we sometimes simplify the hazard ID phase and concentrate on the exposure and other phases. And we have to try to communicate to microbiologists and some others that aren't sort of working in the field why it is important to do that because that is where the uncertainties are, that is where the data gaps are. And that is why it is important to assessment.

(Slide.)

Okay. We talked about in this particular assessment -- we will have comments later -- but the end point being exposure of people to fluoroquinolone-resistant bacteria. That's fine. Good reasons for that, regulatory reasons for it.

But, again, in the larger scheme of drug resistance from agriculture, there are other possible end points as Steve mentioned in his talk. We will look at that at some point. I guess one that keeps coming back to me and I am not really sure how big a deal it is is this notion that there is going to be disease in the community that arises because people are taking drugs for other reasons.

And when they do that, then they are more susceptible to challenge from drug-resistant bacteria. We have got lots of examples in the literature from Salmonella. I don't know about Campylobacter. We can't I think forget that and try to measure it in some way.

And, again, people also talk about the pathogen load phenomenon, gene transfer and the possibility of increased virulence which has come out in different discussions. We have a variety of different hazards that need to be addressed.

(Slide.)

I think another point I would like to make is that in some cases we can focus our efforts on certain components of the ecosystem if you want to call it that, the whole sort of domain of animals, the production systems and processing and so on. And the FDA approach which, again, is appropriate, we focus on the sort of ecological level.

It may be appropriate in some instances to go sort of back in the system and look at other aspects. For example, I am kind of most interested in the pre-harvest phase of animal production. And I think there is a lot that can be done at that level to try to sort of reinforce or further refine the exposure assessment phase of risk assessment.

(Slide.)

And just as one example, one of my Ph.D. students, David Jordan, did some simulation studies looking at in this case not drug resistance, but E. coli 0157 in beef production in Ontario. And he was interested in how different management systems, different ways of trying to mitigate the risk of 0157 might transpire, might sort of feed through the slaughter system in terms of reduced exposure of positive animals in the feed lot.

This is an animal with a kind of heavy tag on his carcass. So basically, in this particular approach which is quite different than the other risk assessments you've heard of, basically it is one of devising a scenario which basically describes the system of beef production and collection and transport to the slaughter plant and says, okay, in an attempt to address what we would happen if we were able to, say, administer a vaccine.

We don't have a commercially available vaccine yet. And it would reduce the quantity of bacteria of 0157 being shed in feces or the prevalence of positive animals in the slaughter plant. What effect might that have on the eventual level of contamination of the slaughter plant? And then he also looked at other types of interventions.

But I guess the point here, as I was saying before, is these are hypothetical. We don't have them yet. But this is a way that we could attempt to identify the impact that they could have. And if it looks promising, invest more resources in research to get them.

(Slide.)

And this is an example of output from Dave's model. And I think the main sort of thing to look at is that on the kind of left side of your screen if you can't read the words, the main thing is the shape of the curve, is that given what we sort of know about 0157, we can bet that just about on any day of the week, there is going to be bacteria coming into a beef packing plant.

But if we are able to test animals and positive lots were either excluded or in this particular case moved to the end of the slaughter queue, then we could shift back in the day the sort of first time that sort of positive animal comes into the packing plant. And this could conceivably reduce the level of exposure, the level of contamination.

It is not a public health measure per se. But it is a bit of information of exposure assessment that could be used in a public health risk assessment.

(Slide.)

I think we also have to acknowledge that there is a lot of different types of scientific expertise that need to feed into this exercise. We have heard about the mathematical and statistical components and the microbiological ones, as well.

We have also got I think to look a little bit more broadly into some of the other areas of biology and so on that have an effect on resistance. We've actually got an expert here -- I haven't met him yet -- Mark Lipsitch I think who works in evolutionary biology with Bruce Levin's group, or had in the past at least. And there is some excellent work going on there in terms of the creation and the selection of resistant organisms in nature.

(Slide.)

So I would just like to follow through on that particular theme. I think we have to sort of, again, look beyond our sort of obsession with real data. I think any of us who have had any kind of medical training or in other fields for that matter want to see some data.

Show us the results. Show us the information and we will believe what you say. But in other instances, it may be appropriate to be less reliant on this quest for data and actually look to theory, look to biology for some ways around these problems.

(Slide.)

And as one particular example of this, Roy Anderson's group in Oxford, has been looking at the temporal changes in drug resistance in human populations and from a theoretical basis is showing that under a constant selective pressure of antibiotic, that we are going to have over time a sigmoid sort of relationship between acquisition of resistance.

And also using these approaches, his same group has shown that with intervention studies -- interventions in this case reducing the amount of antibiotic use in a human population, that we do see a decrease in pneumococcal resistance. But I think the important point from these theoretical studies is that the decrease is much slower to be realized and takes a lot longer and doesn't sort of tail out completely even in the absence of antibiotic treatment or in its reduced use.

(Slide.)

I think in the interest of time, I will finish off with this point. We have got a lot to learn about antibiotic resistance. And I think that we have the same sort of sigmoid curve here where we have got a lot of uncertainty and some particular -- for some particular drugs, some particular pathogens. And for others, we know a lot about the system. We have less uncertainty.

And those of us in the room, the individuals can put ourselves on this curve in different places. But I think the point is for policy-makers, we have to realize that sometimes they are forced to make decisions along various points in this curve. And that is a challenge. So with that I will stop and entertain any questions.

(Applause.)

DR. LONG: Any questions for Scott? Great. Okay. We will go on. The next thing on the agenda is to look at two other risk assessments that have looked at this antimicrobial resistance issue. And to help us to evaluate, to help us put this new risk assessment that we are here to talk about today into context with what others are thinking.

And our first speaker is Steven Anderson. He is currently a AAAS science risk policy fellow in the Epi. and Risk Assessment Division at the Food Safety Inspection Service. And before this fellowship, he was research fellow at the Georgetown Center for Food and Nutrition Policy. While he was there, he got his masters in public policy and conducted risk assessments on antimicrobial resistance in cattle.

GEORGETOWN RISK ASSESSMENT

Dr. Steve Anderson

DR. ANDERSON: Okay. Thanks, Wes, for that introduction. And I wanted to thank the organizers for the opportunity to present our work here today. Do we have a laser pointer?

DR. LONG: We had a laser pointer that was with us earlier today.

(Slide.)

DR. ANDERSON: Okay. I am going to talk about the work that I did at Georgetown University. Thanks a lot. And our risk assessment was -- looked specifically at fluoroquinolone use in cattle. The people involved in the project were myself, Les Crawford who is here in the audience, and another person, Robin Woo. And each of us had particular and distinct roles in this project. And I will discuss more about our roles as we go on.

(Slide.)

I think I should have a slide here actually since I saw several slides today on why chicken. And we should explain why beef cattle because it is not really something that you would think that Campylobacter is an important issue for beef cattle. And you are probably in a sense right.

What we know is that we have several reasons for doing what we did. And I will explain that as quickly as I can. And the first reason is we were aware that the Center for Veterinary Medicine had initiated a study on Campylobacter fluoroquinolone resistance in poultry. So it obviously didn't behoove us to sort or retread their steps.

And at the same time, we felt that an easier system perhaps to work in, although that may have been fallacious thinking, was to start with cattle.

Now, when you think about risk assessments, you think about hazard and risk. The hazard really are those things and characteristics associated with the organism. And then the risks are sort of the outcomes and the human impacts of Campylobacter illness.

I am going to divide the talk into two sections which are the basic parts of the risk assessment. The first one is talking about Campylobacter. We actually predicted first the number of cases that you would get of Campylobacter illness from beef sources. And that really is based on current data.

The next thing that we did was, like everybody else that has been doing these resistance risk assessments, we are treading new territory. Our approach was to really look at trends in the fluoroquinolone resistance data to tackle the fluoroquinolone resistance question. And I will discuss that more as I talk more about the model.

(Slide.)

Okay. I am going to talk first a little bit about the background. But since everybody has presented a fair amount about the background of this organism, I am going to skim lightly over this. So I will be flicking through slides pretty quickly.

The pathogen is a moderate hazard. We are considering mostly Campylobacter jejuni. As was said before I think by Kirk Smith, it accounts for greater than 90 to 95 percent of the human infections that you see.

(Slide.)

And as far as from a processing standpoint, there is limited spread and growth during food processing. And really, a lot of these characteristics affected the way we thought about our risk assessment and the final form of that risk assessment. And you might ask yourself, well, how is that.

And so looking at the first characteristic, there is no growth in food below 30 degrees Centigrade. And that was really limiting as far as our risk assessment. It was great for us because at this point, we didn't have to consider temperature abuse as a real problem. Thirty degrees Centigrade is about 82 to 85 degrees Fahrenheit. It is pretty major temperature abuse before you get growth of the organism.

So we didn't have to worry as much about failures of refrigeration that might occur in the consumer's refrigerator or in transport to the retail setting and other places where refrigeration is important.

The second characteristic and third characteristic, Paula Cray discussed these. It is microaerophilic. And that means that it requires a reduced oxygen atmosphere.

Now, when I am going through this, you might want to sort of contrast and compare in your mind poultry versus beef cattle and how they are processed and why Campylobacter is a real problem for poultry and why it is less of a problem for beef and beef products. And one of those reasons is mainly in the processing.

And that is when you do -- when you look at poultry, poultry are dipped in a chill bath to chill them. A lot of water is there. There is a skin present. They are pulled out of the water. And a lot of that water from the chill bath remains with the carcass in its package. So you have a moist environment for the organism to survive in.

Beef are quite different, the processing. The carcass is hung up to dry. There is ventilation. There is drying that goes on. So the Campylobacter presumably is eliminated in this fashion and through the processing of beef carcass.

(Slide.)

Okay. And we've gone over this earlier today. I am not going to do much with this. Symptoms, you can see gastroenteritis. Most of the cases, again, are self-resolving. In a few cases, a few percent, there is hospitalization and a low mortality.

(Slide.)

The epidemiology, from the literature, we gleaned that four to ten percent of the infections were -- of Campylobacter infections were due to beef. Another thing that made our risk assessment a little easier, as David Vose said, was human-to-human spread is rare. So we can largely assume that Campylobacter is due to animal sources.

The other case that I believe David Vose said made things easier for him didn't make things easier for us. And that is sporadic outbreaks or sporadic cases versus very few outbreaks. And why is this? Well, we looked at concentration. And for us, if you are looking at a lot of sporadic cases, epidemiologists like to get food samples, sample those and see how many organisms were in that food sample to see what dose the person actually received of the organism.

If you have one person here or there getting the disease -- illness and you go back to them and say, "Do you have a sample of that food?", they will usually say, "No, I'm sorry, I don't", or that food has been reheated and it is augmented from that time that they got the original dose.

In an outbreak situation, somebody usually has that food source somewhere. If it is a church supper or whatever, somebody has that ham or somebody has that beef sample that contributed to the illness. The other -- so this makes our job of enumeration a little bit more difficult in figuring out the dose.

The other thing is one infection we presume provides protection. And I will talk about that more a little later on.

(Slide.)

Human clinical treatment, this was discussed earlier. I am just going to say that fluoroquinolones for the most part of the major treatment by default for Campylobacter illness. The other treatment that was mentioned was erythromycin.

(Slide.)

So why fluoroquinolone resistance and why does it occur so often in Campylobacter? For most organisms, it is a two-event process. And you usually have to have a mutation in the gyrase gene or similar genes. And then there is a decreased permeability to the drug.

If you have one of these events, you will probably get an intermediate type of resistance instead of -- you might get one microgram per -- one microgram resistance versus if you have both, you might have resistance at a higher level to four micrograms per ml of drug.

(Slide.)

For Campylobacter though, what you really need is just a single event. And use of that is a mutation in the gyrase gene. And why is that? And usually we think of

<u>Campylobacter</u> as being less permeable to fluoroquinolones.

(Slide.)

Just to remind people, these are the approvals. The human drug was approved in '87, use in poultry in '95, and then just a year ago it was approved in cattle which is our target species last fall.

(Slide.)

Okay. The hazards, people have talked about these before. I don't think I am going to get much into these. You may impeded treatment by 48 hours. And then there is these other factors. Hospitalization perhaps is increased by a half a day or more.

(Slide.)

Okay. This is an overview of our model from the start. It is a very simplified version. And what I am going to present is also a simplified version. I am not going to present a lot of equations and lot of uncertainty analysis for you right now.

I think it is important though just to focus on the components that we included in our model. We looked at the entire population. We presumed 265 million in the United States. All of our assumptions were conservative.

We often favored public health in many of the instances and the other cases that none of these are based on modeling. There is a little bit of modeling involved in the cooking. But we based all of these components on data. So we aren't modeling these components. We are actually basing them on data that we had.

So if you look down this left side, you can see there is this prevalence component. And prevalence contributes equally as well as concentration to dose. And finally, this is the most important thing because dose of the organism is really what we feel is going to contribute to disease.

So if you get a large dose of the organism, say, a million organisms, you are more likely to get illness than somebody that gets ten organisms in their sample of food.

And then finally, what are the infections and outcomes?

(Slide.)

Okay. As far as prevalence goes, we used some data from Norm Stern's group. And Norm Stern also at one time I believe worked on cattle which helps us out a lot. And we took a sample, 360 samples in the retail sector, and determined several different data points. So we had 90 samples each times four at different times of the year.

We took those and generated a distribution for prevalence. So, basically, the prevalence goes from one percent to seven percent. And our model reflects that diversity of results that he has in this distribution.

(Slide.)

And then the next thing was concentration in ground beef. And, again, if you look at the data from these points, you will see it is in the early '80s. Well, at this time, I don't think Campylobacter had the prominence in poultry that it now has.

It was probably in the late '80s and the '90s when we determined that chicken is probably the major carrier of this organism and the major problem. So a lot of these data are a little bit older.

So Mike Doyle's group actually provided these four organisms per gram in several samples, about less than a half a dozen. We used that as our major point. We used a triangular distribution starting from one organism per gram. And we presumed that the highest point would be ten organisms per gram and that the most likely would be this four organisms derived from Doyle's data.

(Slide.)

So we've done prevalence and concentration. I am going to relate this to you later in the final result. Now, looking at the preference for rare, just backgrounding that, I am going to say that these are the individuals that like rare meat, are the ones that are going to be at highest risk for Campylobacter from hamburger and ground beef. And we are also going to look at the reduction of those organisms in those samples due to cooking because cooking has a major effect. So this is the predictive microbiology portion of the talk.

(Slide.)

Consumer behavior, those that like improperly cooked -- there are several studies out. We integrated a number of these studies and developed this beta distribution to represent those studies. The mean values is around eight -- anywhere from 17 to 18, 19 percent, so in there. So about 18 percent like their burgers cooked medium to medium-rare or rare.

(Slide.)

Our cooking assumptions were made, again, from the literature, was that Koidus and Doyle found that heating at 60 degrees for two minutes caused a million-fold reduction in the number of organisms, so a six log reduction, a major reduction. And that would pretty much eliminate any organism that you would see in a hamburger patty.

Unfortunately, most people don't cook entirely to this temperature for that long. We modeled based on 50 to 60 degrees which is the temperature range that most people cook at and this being down at the rare side or even below rare. And then this being up on the more medium to well side.

We also modeled -- based specific times and temperature, 15 seconds to 20 minutes that they would cook in this range. And let me show the results of that work.

(Slide.)

That modeling showed -- and we derived the thermal death times from a zero kill up to a six log kill, so a million-fold reduction. And on average, the most common reduction would be a 4.3 log reduction. Now, what does that all mean?

(Slide.)

Just sort of averaging that all out, even improper cooking will reduce Campylobacter by an average of 20,000-fold. It's a pretty major reduction when I show you how many organisms people will be exposed to.

(Slide.)

Again, the people that are going to be most susceptible and have the greatest problem with Campylobacter are going to be down here in the small tail of this distribution, those that like their bloody rare hamburgers and their rare hamburgers.

(Slide.)

So the greatest at risk are those three to five percent that like the rare meat. Even down there when you decrease it 500-fold, which is $10^{2.8}$, you are still going to have the chance for organisms to be present based on our consumption analysis.

(Slide.)

Okay. So we are down here at dose. And we are going to analyze the amount of hamburger that people consumed based on USDA data.

(Slide.)

We determined this is an average of 57 grams per ml. And this is based on the consumer survey for food intake which is a large survey done by USDA which is I believe now greater than 12,000 individuals involved in this study. And we did a custom distribution which I can't show you because it is quite diverse. It goes from one gram up to 2,050 grams. So you have people out there eating 2,000 or more grams of beef. But for the most part, the average person eats about 57 grams per meal.

So based on that if you have a maximum of ten organisms in that food, this should be before cooking, you may have 570 organisms, 10 times 57, or you may have zero if it is cooked well, or you may have more if that person with 2,050 grams has -- is eating a positive sample of beef.

(Slide.)

Okay. So what's next? Next you say, well, how do I sort of take that number that I've got for the dose which was that from the previous slide, this amount of organisms that they could have eaten. You put that into a relationship which predicts infection based on the amount of organisms a person ate. And this is a probability of infection. And this is a beta Poisson distribution.

And based on this study that was done -- I should explain a little bit about that. It was a volunteer study done on 110 individuals. And then Medema analyzed and derived this equation from this study that was done at Johns Hopkins.

Now, for illness and outcomes, that was a little more difficult. We decided to use an estimate, professional expert opinion estimates based on Martin, et al. in 1995. And those predict the potential outcomes for infection and illness. Okay?

(Slide.)

Let's see. Outcomes, our outcomes -- I am just going to go quickly through this since I am almost out of time. The infected individuals, we predict 15,700. The number hospitalized, 150 and about three to four possible mortalities. The range is 76,000 to 190,000 for the CDC estimates. We have this difference with the CDC -- oops, sorry.

(Slide.)

But we have a large uncertainty in our values. So this is getting closer and closer to the CDC values. Actually, 66,000 versus 76,000 or more. And also, there is not uncertainty with these numbers. So these could be lower actually than they appear. So hospitalized and mortality.

Let me get through to the --

(Slide.)

Fluoroquinolone resistance, we did a trending study. You can just sort of read through this. Used resistance data from various countries including countries with restricted usage. We started at year zero when the drug was approved for use in the veterinary setting.

Year zero, 1.3 percent. It actually could have been lower. We have some other references that say as low as zero percent in one year. The first year, one to eight percent was the range. The second year was three to 11.

(Slide.)

Sorry to be rushing through, but I want to get through to the end. Three years, it went from eight to 12 percent. We are using data from these three different countries. And then the Netherlands, 11 and 29 percent. And then also, the worse case that we will present.

(Slide.)

So where does this all get us to? In the 1,000 individuals that we predicted would seek treatment, in the first year, ten to 80 of those would be affected by fluoroquinolone-resistant organisms due to the consumption of beef, 30 to 120 in the second year; the third year, 80 to 130. Again, eight percent to 13 percent.

The number hospitalized would go in a similar fashion. We wouldn't expect to see mortalities at this early stage.

(Slide.)

Again, I am not going to go through this. But, again, you see the trend going up. And in the worse case scenario, the trend goes up. By the tenth year, 40. And then you may see a death associated with fluoroquinolone resistance in the tenth year of use of the drug.

(Slide.)

Okay. The values of risk assessment, I think these are probably the most important things. And I think people have talked about these enough. But I am going to say that probably the most important thing is this for this audience which is it provides a framework for dialogue. And it provides a joining point for us to compare how we believe.

And you can look at my model and say, "You know, I don't agree with you on this number or that number or how you treated that." And we can discuss that. And I think that is important in this sort of acrimony that tends to flow in these antibiotic resistance meetings.

(Slide.)

The people that were involved in the advisory committee that helped us formulate our problem and focus it: Doug Archer, Jerry Brunton, Russ Cross, Ana Lamerdine, Abigail Solures, all different people with different sorts of expertise. The person that developed our spreadsheet was Lehla Burrage from Novadin Sciences in conjunction with Barbara Peterson.

(Slide.)

And the study was funded with the Animal Health Institute's help, and also with Georgetown University's. Thank you.

(Applause.)

DR. LONG: Okay. Is there one quick question for Steve? Can you go to the microphone?

MR. : Just real quick.

DR. LONG: Okay. Go ahead.

(Away from microphone.)

MR. : You made a comment about --- people ---.

DR. ANDERSON: Right.

MR. : Could you say a little more about that?

DR. ANDERSON: In the literature, generally it has been shown that people have one exposure to Campylobacter and they are protected for a lifetime, although they may be infected. They may eat another, say, Campylobacter-infected hamburger. They may get infected by that which means they will shed it in their stool. But they likely won't get illness from that. And that has been shown in the Black study as well. He found people also with second exposures, that they would shed but not become ill.

DR. LONG: Okay. We will move on. The next speaker is Louise Kelly. She works at the Veterinary Laboratories Agency, Department of Risk Research in Glasgow, Scotland.

She is responsible for all the risk assessment modeling undertaken by their department. And this includes a broad range of different types of risk assessment models, import-export risk assessments, ecotox. risk assessments, disease transmission modeling, food safety risk assessments, and antibiotics resistance, scooping studies and assessments.

EMEA RISK ASSESSMENT

Dr. Louise Kelly

DR. KELLY: I just achieved being more than four-foot, ten. I have reached five. So I hope you can all see me now. And thank you very much for inviting me here today to take part in this workshop. And what I am going to present to you today is the work that has been done by ourselves at the Veterinary Laboratories Agency in the U.K. for the European Medicines Evaluation Agency.

And this work was done by my boss at the Veterinary Laboratories Agency, Dr. Marian Wildridge. And I am going to present her work to you today.

(Slide.)

So the main focus of this study was to look at one particular problem in relation to antibiotic resistance. And that was to look at problems associated with Salmonella typhimurium and with fluoroquinolone-quinolone class of antimicrobials. So in this particular study, we had to look at one particular organism and one particular class of drugs.

(Slide.)

The study was based on a two-week period. So it was a very short study that was undertaken. And the impetus for this work arose as a result of a vast amount of data that had been collected by the EMEA. So the first aim of our study was to evaluate that data that had been collected. So the study was based on that data and that data only. No other information was collected from any other source.

(Slide.)

Following this evaluation, the second aim of the study was then to extract from this data any data inputs that would be relevant for a risk assessment and in particular, a risk assessment for Salmonella typhimurium and fluoroquinolones.

(Slide.)

Then the third and the main aim then was to present these major inputs, extract it from the way that the data was presented to us in the form that would be relevant for a qualitative risk assessment. So we are talking in terms of qualitative assessment there rather than the quantitative approach that we have been discussing up until now.

Given this extraction then and the search for data inputs, the next main aim was to look at problems associated with the data that had been supplied, so particular problems with the EMEA data irrelevant of any other information that may have been collected from elsewhere.

In relation to this, we would be looking for data efficiencies, inappropriate data collection with specific regard to risk assessment modeling and any areas of missing data, again, for this particular data set.

Then if possible in this very short two-week time period, the aim was to qualitatively assess the risk for one particular risk question, make recommendations on further work that should be undertaken both by the EMEA and any other groups that may have been involved here. And this would be with regard to future data collection and, in addition, risk assessment methodology, both from a qualitative and a quantitative perspective.

(Slide.)

So what we want to look at now is the qualitative risk assessment that was undertaken. So if you remember, I had mentioned that this was done -- the agreement was to do this if it was turned out to be possible in the short time frame. And it was found that some information was available to undertake a short qualitative assessment.

(Slide.)

So today we have been talking about quantitative modeling. How does this differ from qualitative risk assessments and when should we focus on taking this approach rather than the quantitative steps in the first instance? So here we will have just a basic reminder or an introduction to this for those who are not familiar.

(Slide.)

The first and most important step that we found in this process was to define the exact risk question that we are trying to address. And this has been mentioned today in relation to the CVM model. We have to both agree with the assessor and the manager what is the exact question that we are trying to address here. So our first step was to agree with the EMEA what exact question we would be looking at.

(Slide.)

We then move on to elucidate pathways from the particular hazard that we are interested in to a particular unwanted outcome.

(Slide.)

For each step on the pathway gather the data to assess an overall probability first for each step and then for the overall risk that we are interested in.

(Slide.)

And this for a qualitative assessment would be assessed in terms of words such as low, medium, negligible or high. And these are words that are commonly used in risk qualitative assessments.

(Slide.)

So the case study that we were looking at, Salmonella and fluoroquinolone group of antimicrobials.

(Slide.)

The question that we were posed to address by the EMEA, a rather large question here, but essentially it is looking at the risk of adverse human health effects in the European Union only consequent upon the development of antibiotic resistance to fluoroquinolones due specifically to the use of these drugs in farm livestock.

And you will notice here we are not identifying any particular species such as poultry, cattle, pigs. In this first case study, they wanted us to consider all livestock species.

(Slide.)

So our first step based on this risk question was to consider an appropriate or a possible risk pathway to describe in which antimicrobial resistance could be transferred from the farm to the human and have an adverse human health effect. We decided in the first instance to go down the traditional route of the farm-to-fork type approach and map out the different stages that would be necessary in this element.

(Slide.)

So looking at the key stages of the transfer from the farm to the fork and to the human health effects.

(Slide.)

So we began by looking at resistant organisms present in farm livestock. And here we are defining these to be Salmonella typhimurium-resistant organisms to the fluoroquinolone group, then moving on to see how this would transfer from the farm to result in a human exposure to these resistant organisms.

(Slide.)

Following exposure, humans could then either be infected or colonized with resistant organisms. And then this would lead on to an adverse human health effect.

(Slide.)

So our aim was to look at each of these stages in turn, evaluate the EMEA data, and determine how much could we actually use to estimate in a qualitative manner the probabilities that would be necessary to describe these various stages.

(Slide.)

So Stage 1, resistant organisms in farm livestock. Essentially, here our real aim would be to assess the probability of the presence in farm livestock of resistant organisms due to the use of these drugs. And from the EMEA data, we were able to first of all assess in the first aspect presence of Salmonella typhimurium infection.

(Slide.)

And we find that throughout the EU, the data that had been supplied suggested that such prevalence was both variable between different countries and between different livestock species.

(Slide.)

There was a large amount of missing data in this one data set that would allow us to properly interpret or properly estimate a level of prevalence.

(Slide.)

Overall, we concluded that the prevalence of Salmonella typhimurium would be low, but there was a high degree of uncertainty associated with this data.

(Slide.)

We then, following prevalence, attempted to look at, well, if an animal is infected or colonized with Salmonella, then what would be the probability of those organisms being resistant to fluoroquinolones.

(Slide.)

It was complex and contradictory data for this aspect model. Again, variation between different EU countries and species of livestock. There was missing data again and there was a large range reported, again, for the different species and different countries ranging from zero to 86 percent in some cases. Again, overall we concluded it would be low; but, again, a high degree of uncertainty.

(Slide.)

So our overall conclusion for this first stage, how likely is it that resistant organisms would be present on the farm, overall we concluded that it would be low, but with a high degree of variability and uncertainty with regard both to countries and different species.

(Slide.)

So for Stage 2, human exposure to resistant organisms, we have assumed that these resistant organisms have originated on the farm and by some mechanisms, exposure through ingestion is going to result. So for this stage, we would have to look at all stages of the production process and then preparation, cooking in the home of the consumer.

(Slide.)

So our end point here would be to assess the probability of human exposure to these resistant organisms resulting from farm livestock. And the main point that we found here from the data provided, that we could not assume that all resistant organisms present on the food source came from the source animal. The information the EMEA provided did not allow us to assume that.

(Slide.)

So ideally, for this stage, we would have likened to consider each step on the production process an attempt to estimate the probabilities. And we found that this was very difficult to do. So we had to approach it from a different way.

(Slide.)

And instead of trying to estimate the probability of transition of organisms, we looked for data at each end of the food chain position to see what the probability of isolation would be. So we found again it was very little in this case between different stages of production for different livestock species and, therefore, different types of food product, and again within European countries.

(Slide.)

Missing data, again, particularly in different serotypes of Salmonella, overall probability of isolation at any one stage seemed to be low. But, again, very much a high degree of uncertainty.

So given, again, that we considered to some respect the probability of isolation at the different stages of production, how then would preparation in the world of the consumer have an effect on the probability of final exposure?

(Slide.)

This aspect of the exposure process had not been properly addressed within the data collected by EMEA. There was a very limited amount of information to assess in any respect this probability.

(Slide.)

Overall, it appeared that the probability of cooking reducing the level of exposure would result in this significant type of reduction. But this was all we were able to conclude from the information provided.

(Slide.)

So, overall, the probability of ingestion and, therefore, exposure to these organisms, again, low we concluded, but a high degree of uncertainty.

(Slide.)

Variable again between country and species. And, therefore, again, we are looking at a problem with much variability and much uncertainty.

(Slide.)

So Stage 3, given exposure to CARS, then what is the probability of either colonization or infection? For this stage, we are interested in the probability that the Salmonella typhimurium organisms from animal products going through the food chain would actually result in some kind of infection or even colonization.

(Slide.)

Again, the information provided to allow us to do this, for example, in a dose response type approach was very, very limited. So, again, we had to approach it and look for information in a different manner.

(Slide.)

So in this case, we looked for information that would suggest that there was any relationship between human and animal isolates reported in the literature.

(Slide.)

The reported conclusions were equivocal and, therefore, we could not automatically assume that these isolates had originated from farm livestock. Again, this was from this available data.

(Slide.)

Following on from this, we then looked to see, well, what is the actual probability of any randomly selected individual in the country being reported as a case of Salmonella typhimurium infection.

(Slide.)

And from this data, this suggested to be low and in some countries it was very low. But, again, there was variation by country and, again, uncertainty. And much of this uncertainty arose due to the differences in the reporting systems and, therefore, in the differences in the availability.

(Slide.)

But what we found from the information was that even where reporting was mandatory, the probability still appeared to be low.

(Slide.)

So our final stage of this farm-to-fork type model and adverse human health effect, what is the probability of such effects given ingestion and subsequent infection or colonization with resistant Salmonella typhimurium?

(Slide.)

Again, a limited amount of data allowed us to estimate this in a way that we would normally do in the farm-to-fork type approach. So, therefore, we looked at human isolates and the data that would allow us to estimate the probability of those isolates actually being fluoroquinolone resistant.

(Slide.)

David suggested that this was generally low, although there would be appear over the years to be a suggested increase within the U.K.

(Slide.)

Again, it was suggested that more data really here would be required to reduce large amounts of uncertainty. Given then that human -- a random individual may be regarded as a human isolate or fluoroquinolone-resistant, then what would be the probability of this resulting end treatment requirement? This was suggested to be low, but it may be higher for resistant strains than for non-resistant strains.

And the suggested range in the data provided was around ten to 36 percent, so a large amount of uncertainty again.

(Slide.)

So the overall risk from these different stages, trying to combine these, what is the probability of an adverse effect, we concluded from each stage that each stage has a low probability of occurrence. And for most stages, there were some data available to quantify perhaps at a later date.

And for some stages, data was particularly sparse, in particular from the probability of the food point at the point of ingestion actually being contaminated with resistant organisms and the probability of strains isolated from humans being the same and, therefore, coming from strains from livestock.

(Slide.)

So the overall quantification, again, variability due to species and country, large amounts of uncertainty in missing data in particular, with regard to serotypes, denominators and reported methods of isolation. But overall, our initial qualitative assessment suggested that the probability would be low, a large amount of uncertainty and variability.

(Slide.)

So this very short study, what did we conclude from this? A number of recommendations were made. First of all, a risk assessor should be appointed to work closely with experts in the EMEA if any further data has to be collected. So a large amount of data was collected, but none of this was done with the view to undertaking a risk assessment.

(Slide.)

The data sources provided should be revisited in a much longer period of time rather than two weeks. And this should be done with an understanding of risk assessment. And that would allow some estimation of uncertainty.

(Slide.)

It was suspected that there are much data in existence for this probable. But it is not actually available in a format that could be required to allow us to input into either a qualitative or a quantitative assessment.

(Slide.)

So a revised qualitative assessment should be undertaken at some stage to indicate genuine data gaps and, indeed, to consider one more specific question that was undertaken in this study in particular for one livestock species and perhaps for one European country. And then at a later date if appropriate, a quantitative assessment should be undertaken --

(Slide.)

-- concurrently with data collection, perhaps a Stacastic model and would allow an updatable tool to use in a regulatory fashion as the one presented today. Thank you very much for your time.

(Applause.)

DR. LONG: Thank you, Dr. Kelly. I think this is a great example of the use of qualitative risk assessment to help us focus in on what our problems and data gaps are without going through the large quantitative exercise as an immediate first step. Are there any questions? Okay.

We are scheduled to go into a break. And as you may have noticed, we are a little bit behind. And Dr. Sundlof promised we would be out of here by 6:00. I am going to do the best I can during the panel discussion to keep us on track there and maybe trim a minute off of each person so we can make up about eight minutes.

If we take a ten-minute break instead of a 15-minute break, then we can gather back another ten. And 6:00 is still a distinct possibility. So it is 3:00 now by my watch. Back at 3:10.

(Whereupon, a brief recess was taken.)

DR. LONG: The next item is looking at the risk assessment, assumptions and uncertainties by Kathy Hollinger who is a veterinary epidemiologist and by Mary Bartholomew who is a mathematician/statistician both for the Center for Veterinary Medicine. I think that their talk will be important as we move then on into the panel discussion and address the questions that are listed on your agenda. So this is going to be a tag team here. So Mary is going to start us off.

CVM RISK ASSESSMENT: ASSUMPTIONS AND UNCERTAINTIES

Dr. Kathy Hollinger and Mary Bartholomew

MS. BARTHOLOMEW: Good afternoon.

(Slide.)

I hope you have had some time since lunch with the break and everything to get your serotonin levels back up to an acceptable point. And so on that assumption, I am going to get started talking about the assumptions and the statistical uncertainties in our risk assessment.

There are two different sorts of assumptions that are used in this model. The first sort is the type that is used when there is a lack of data. For example, there is information about the rate of seeking care among people with all sorts of diarrheal disease. There is not that same information about the rate of seeking care in patients with Campylobacteriosis.

So we had to make an assumption at that point. So that is one type of assumption. You don't have the data in the specific population of interest. So you make an assumption you can apply the same rate that you have got in a given population to another.

And then the other sort of assumption is a statistical assumption. We have data in the appropriate population, but it -- the parameter of interest is not known with perfect knowledge. So we make the assumption that given the data that we have got, we apply a particular statistical model. And that is our assumption, the given statistical model, to generate the uncertainty distributions about the parameter of interest.

(Slide.)

So I am going to talk about a couple of the global assumptions of the first type. And then I will turn it over to Kathy. She will talk about some more of those. And since there is a lack of data involved, she will also consider some of the data gaps.

Our first global assumption is that susceptible and resistant Campylobacter have the same virulence characteristics. At the time that we started the risk assessment model, that is certainly what we thought. And as was mentioned earlier this morning by Dr. Angulo, there may be some indication of a difference -- that this is not true in the future.

So we will be looking for more information when it becomes available. And if that happens, we will have to modify something in the risk assessment.

(Slide.)

We also assume that susceptible and resistant Campylobacter have the same survival characteristics from slaughter to the point of human exposure. Again, we have no indication that that is not the case.

(Slide.)

We also made the assumption that human susceptibility to infection remains constant in the population.

(Slide.)

And that consumption patterns remain constant. And in the short time frame that this risk assessment covers, that is probably true. But you have also heard some information from Dr. Cray earlier this morning that, in fact, if you look over a wide enough period of time, that is not true either.

Well, as we said, our risk assessment model is fairly simple and it is flexible. If we find out different information that leads us to believe that these assumptions are not true, we will update it. And I will turn this over now to Kathy. Dr. Hollinger will cover some of the other fine points of the data assumptions.

(Slide.)

DR. HOLLINGER: So I get to give the top ten list so to speak, but in reverse of David Letterman's grouping of the -- his top ten list. Our risk assessment model modeled the measurable human health impact of fluoroquinolone-resistant Campylobacter jejuni and coli that were acquired from poultry sources using the most currently available data to model that risk.

(Slide.)

The assumptions I have listed here in order of priority in the model, the impact in the model from my perspective, not necessarily from a mathematical perspective. The first assumption, the one with the most impact on the model, is that fluoroquinolone resistance in people calculated after we removed those people who traveled, those people who used fluoroquinolones prior to culture, and those for whom the time of fluoroquinolone use was unknown was attributed to chickens.

And we removed travelers because it is known that travelers carry very frequently higher levels of resistance than the general population. They don't acquire their disease in the United States. And, therefore, their disease was not tied to domestic drug use in food-borne sources.

Fluoroquinolone use is associated with development of resistance so that those people who had cultures taken after they had used a fluoroquinolone could possibly have had a resistant infection due to that use. And those people for whom the time of the fluoroquinolone use was not known could have then had their fluoroquinolones prior to taking cultures.

So that remaining resistance then was attributed to chickens. And we use the Campy case control study to be able to determine what proportion were travelers and who had used fluoroquinolones and those who did not know when their fluoroquinolone was used.

(Slide.)

This assumption represents a data gap. The remaining level of resistance could have been distributed either uniformly across all sources of human infections that were remaining or that resistance could have been attributed to a single source or to certain specific sources.

So this assumption was based upon evidence of fluoroquinolone resistance developing in chickens, humans and when fluoroquinolones are used because there was no food animal fluoroquinolone use other than the use in poultry until late 1998. And there was no fluoroquinolone resistance observed prior to '92 in human cases in the U.S. even though fluoroquinolones had been approved for human use since 1987.

We felt it was unlikely that the increase in domestically acquired fluoroquinolone resistance that was observed in people since 1996 as reported in the Minnesota paper that was published in May of '99 could be attributed to levels of resistant Campylobacter that were uniformly distributed amongst all sources of human infection.

The distribution of resistance in food-borne sources of infection was more likely to be associated with specific exposures linked to drug use and was assumed to be limited predominantly to poultry.

(Slide.)

Assumption number two states that the level of risk ascertained in the early 1980s represent the current level of risk in the U.S. population. And this is the risk of acquiring a poultry associated infection. And we modeled this estimate. And we used the literature. And the proportion of cases that could be attributed to exposure to chicken was 48 to 70 percent in the literature.

This wide range was modeled with a uniform distribution to account for the large amount of uncertainty in this parameter. The CDC is currently analyzing a case control study evaluating risk factors for Campylobacteriosis which we expect will provide an update of this estimate and maybe a more precise estimate.

(Slide.)

Both assumptions one and two represent data gaps in, you know, precision of estimates and the proportion of human disease attributable to the specific source of infection and then how to determine the level of resistance in specific food-borne sources of infection.

(Slide.)

Assumption number three, we had some data for the level of resistance that was observed in broiler chickens. And that data was a sample of only 159 isolates that were collected in a pilot survey. And the collection period was limited from October to December.

The level of resistance in chickens was modeled using the level of resistance in Campylobacter jejuni species alone as there were no data available that were specific to Campylobacter coli.

This may have slightly under-estimated the level of resistance. But because Campylobacter coli represents such a small proportion of human disease, only 2.7 percent in the NARMS isolates in '98, it was unlikely to have much, if any, impact on the overall estimate of the risk.

A prevalence survey is currently being conducted by FSIS that will provide a more robust sample for isolate susceptibility testing in 1999.

(Slide.)

The next assumptions have been grouped together because Campylobacter-specific data were not available for the proportion of enteric cases that sought care for either bloody or non-bloody diarrhea for those cases that were requested to submit a stool and did submit a stool for culture for both bloody and non-bloody diarrhea and for the proportion of people that received treatment but never submitted a stool sample.

Rates for these parameters were obtained from population surveys conducted by CDC at FoodNet sites for diarrheal illness or from a survey of physicians that saw patients for diarrheal disease. And I will give one example of the seeking cure assumption.

(Slide.)

This assumption states that the rate of seeking cure among people with diarrheal illness is similar to the rate of seeking cure among people with Campylobacteriosis. And then this assumption was divided into two components, one for bloody diarrhea and one for non-bloody diarrhea because the rates of seeking care were expected to be different.

Bloody stools were significant risk factors associated with seeking care in a multi-variate analysis of the population survey data. The rates of seeking cure were obtained from the population survey for persons with diarrheal disease. And diarrheal illness was defined as three or more lose stools within a 24-hour period or diarrhea lasting for more than one day or which resulted in an inability to perform normal activities.

And as a validity check or a cross-check to see if population data could really apply to these parameters for Campylobacteriosis, a comparison of symptoms significant in seeking care for diarrheal illness in Campylobacteriosis was made to determine if this rate was applicable to these Campy rates.

Comparing the groups, a greater proportion of people with culture-confirmed Campylobacter cases were affected by fever and blood in their stool than the people seeking care for diarrheal illness. Therefore, the actual rate of seeking care for Campylobacteriosis may be somewhat under-estimated.

However, because a greater proportion of people with fever and bloody stools would be cultured and possibly enrolled in the case control study, it makes such comparisons somewhat difficult.

(Slide.)

Our next assumption was that the incidence rates for culture-confirmed Campylobacter infections in FoodNet catchment are representative of incidence rates for culture-confirmed Campylobacter infections in the United States. We compared demographic characteristics of the FoodNet catchment area population to the U.S. population. And we looked at characteristics available from the U.S. Census Bureau.

And some of those are rural to urban population distribution, age, sex and race. And these characteristics were similar except for fewer Hispanics were represented in the FoodNet catchment area than were in the U.S. population. And we felt that because this comparison of demographic characteristics was so similar between the FoodNet and U.S. populations, that this indicated risk factors for the disease may also be distributed similarly.

And, therefore, rates of disease obtained from FoodNet would be likely to be representative of disease rates in the United States. And the table comparing these demographic characteristics is available in Section 1 of the risk assessment.

(Slide.)

Again, we group these assumptions 11 through 13 here because data were not available to describe invasive disease parameters. The invasive disease parameters that we were looking for were the proportion of cases seeking care, the proportion of cases that were requested for and submitted specimens, the sensitivity of culture methods and treatment rates.

Invasive disease is predominantly bloodstream infections and bloodstream culture methods are a fairly good method for isolating Campylobacter. And we felt that probably most of these invasive cases would be detected -- first of all, that they would seek care; that they would be detected through these culture methods; and that they would be treated with an antimicrobial.

Because invasive disease cases represent less than one percent of overall number of cases, we felt that even if we were slightly under-estimating or over-estimating the total number of cases, that it would have very little impact on the overall risk.

(Slide.)

Assumption number 14 was the proportion of people not submitting a specimen that received antimicrobials for treatment of diarrheal disease was similar to the proportion of people with Campylobacteriosis that didn't submit a specimen and were treated. We didn't have a data parameter for that from the Campy case control study because all of the cases that were included there were culture-confirmed cases.

So we went to the population survey and looked, again, at diarrheal illness and found that those people who don't submit a stool sample were treated at a rate of around 40 percent compared to the culture-confirmed cases who were treated at a rate of 84 percent.

(Slide.)

Assumption number 15 looked at the proportion of people treated with fluoroquinolones. And we used that to -- and it was the same for people with enteric disease and people with invasive Campylobacteriosis and enteric Campylobacteriosis that did not submit a stool for culture.

Again, the treatment rates using fluoroquinolones were obtained from the Campy case controls data. And, again, those were culture-confirmed cases and invasive Campy. And for those people who did not submit a culture, we needed drug use information. And then we assumed that they would be treated at the same rate as other individuals with enteric disease. Okay. Mary.

MS. BARTHOLOMEW: As I alluded to earlier, the second sort of assumption was applied in considering uncertainty distributions. When we didn't know -- when we didn't have perfect knowledge of a population parameter, we would want to estimate the uncertainty that we had about it.

It would be in the specific population of interest. But we still needed to show that. We had only a sample out of the total population.

(Slide.)

So we had to model the -- we had to model -- make an assumption about the statistical model that would be appropriate for doing so. So, for instance, if we had a proportion like the proportion of people seeking care that we wanted to model, we assumed that that binomial proportion was, in fact, a beta.

If we did not, in fact, have the real proportion, for instance, if the p that we were given -- the estimate for p being the proportion that we were seeking -- was a weighted estimate such as from a population survey, sometimes a population survey is done in such a way that the different areas that are sampled are disproportionate. So then the surveyors will adjust by giving you a weighted proportion.

Given the weighted proportion, we didn't have a numerator. So what we did was we took p* which was the given weighted estimate based on a sample of size n, and then we back calculated and said the success rate for that given p* would be n times p*, or s*, s* being the number of successes, the numerator that we didn't have.

And then we modeled p using that s* as a beta, s* plus one which is the number of successes plus one and the number of failures plus one. That is a kind of standard assumption for modeling binomial proportions.

(Slide.)

I will go down a laundry list more or less for the different output variables. When several variables are strung together to create an output, then the output has the product uncertainty. So this was the output that Dr. Vose showed for the total number of Campylobacteriosis cases in the United States for 1998.

And as he mentioned, we should think of this not as the distribution of the number of cases, but as the expected mean. So that the mean could be anywhere from about 0.9 to about, what is it, nine something -- I can't read those numbers from here. But anyway, you can see what they are. And so that is not an estimate --

(Laughter.)

You can't? Oh, dear. I will tell you. It looks to me like 4.8 is kind of up there in the tail. Anyway, I will tell you the laundry list of the variables that were included. We had to incorporate uncertainty about the proportion of cases with enteric and bloody stools, and the enteric with non-bloody stools or those that had invasive disease in the first place.

Then we had to determine the proportion of each of those types who sought care and the uncertainty distributions about those. We had to develop the proportions of each type who requested -- who were requested and did submit culture specimens and the uncertainty distributions about them and the proportion of cases that were tested who were actually ascertained to be positive by the culturing procedure.

So that this estimate here involves the uncertainties from those four different -- five different sets of proportions.

(Slide.)

This is the output variable for Section 3 which ways the fluoroquinolone-resistant Campylobacter infections from chicken that received fluoroquinolone as treatment. And the laundry list of variables of uncertainties -- whose uncertainty distributions had to be included were proportion of Campylobacter due to chicken consumption, proportion of persons seeking care, proportion of those seeking care who receive antibiotic therapy, proportion of those receiving antibiotic therapy who have received fluoroquinolone and the proportion of infection from chicken that are resistant.

(Slide.)

And then finally, we have the output variable for Section 4 is the nominal mean total number of people with fluoroquinolone-resistant Campylobacter infection from chicken that we see fluoroquinolone as treatment. And the uncertainty in that variable comes from the prevalence of Campylobacter on chicken carcasses, the prevalence of resistance among Campylobacter isolates in the slaughter plant, the prevalence of fluoroquinolone-resistant Campylobacter on carcasses and amounts of chicken consumed.

And so naturally the probability distributions that you were shown as the final analysis in Section 5 depend on all of the above. And that pretty much describes how we dealt with model uncertainty. Thank you.

(Applause.)

DR. LONG: Okay. These two are ready to take questions. I think they have tried to lay out the assumptions and the uncertainties. And we are interested in what you have to say. Please, if you can line up behind the microphone, that would be great.

MR.   : I would like to ask just about a couple of further uncertainties and assumptions that you may be making. The first is that any chicken Campylobacter is the same as the Campylobacter that will cause infection in man. Although there clearly are cases where this thing can be made, I think there are many cases where it can't.

And as I understand, the distribution of Campylobacter in chickens doesn't by any means relate very closely to the distribution in a population from humans. That was the first one. Would you like to make a comment on that?

DR. HOLLINGER: Yes. I think that the Campylobacter on chickens very closely parallels the Campylobacter that we find causing infections in people. We have seen strain typing -- first of all, the list that Dr. Cray offered earlier today, if you look at the species level, the predominate isolate from chickens is Campylobacter jejuni. And you find that isolate in human clinical cases.

And if you want to look at the -- you know, looking at strains within Campylobacter jejuni, you can type strains by many different methods. And when you do strain type by either the biotyping, serotyping, or even using a PCR or some of the other RFLP techniques, you find that very -- there are -- there is a lot of overlap between human, poultry and cattle strains. And that is a recent paper out from Denmark.

And then you find a little different association from the Campylobacter coli. You find similar strains amongst swine, people and chickens. So I would say that the evidence is there. It is available in the literature. And it shows that the strains very closely do overlap between humans and poultry.

MR. : Is the question of the burden of contamination of the chicken carcass something that you are taking an assumption about, that any organism whether present in tens, hundreds or millions is equivalent regardless?

DR. HOLLINGER: We have a table in the risk assessment that shows the burden of contamination. The most probable number in the case of this survey, the FSIS baseline surveys, because they used enrichment procedures. And the burden of Campylobacter on chickens is considerably higher than any other food animal species that was sampled.

MR. : But you nevertheless have to assume that any contamination is equivalent to any other in your -- in the way you take these into account, do you not?

DR. HOLLINGER: David, do you have a --

(Away from microphone.)

DR. VOSE: --- but mathematically, it is looking at a quantity of --- and post-slaughter, just the chiller. And if it is infected with --- Campylobacter, then it doesn't really matter from the point of view of the mathematics what the number of bacteria there are in that sample. Clearly, it does matter when it comes to feeding that to a person because a large amount of bacteria, the more likely they are going to be ill of course.

But if the distribution of the number of bacteria that will be in contaminated carcasses remains constant, then the mathematics of this problem remains constant, too.

If the distribution changes so if we were to institute some risk management technique that reduced the load, then we would have to make a change in our model which I think turns out to be a reasonably simple thing to do under a certain --- unlimiting assumption. But it does point at -- it is not necessarily considered a given item --- how many Campylobacter ---

MR. : My final point is this one to do with the seasonality. As I understand it, the reason for this seasonality is far from clear. But it is very dramatic as we saw this morning. I wonder whether this really does raise a question about our knowledge of the epidemiology of this organism which suggests that maybe we are assuming a simplicity of connection here which maybe turned out to be misplaced in time. Thank you.

MS. BARTHOLOMEW: I think the important thing about that is that we are looking at an annualized rate. And so that if there are peaks and valleys, it is really sort of the annualized rate that we are modeling. And if there are significant shifts in that annualized rate, they will maybe have some peaks and valleys.

But if the peaks and valleys increase the following year, then the annualized rate the following year will also increase.

MR. : There is something odd going on

though.

MR. CONDON: Yes, Robert Condon. It may affect your estimates to just that seasonality depending on these case control studies. The question I wanted to address was your estimates of the portion of cases coming from poultry chicken primarily and the case control studies that you used. And the values there are based on the factors they looked at. In the Colorado study, they only looked at it as reading a summary, only two things.

So the fact that you got 70 percent out of that study to me doesn't mean anything. If you only look at pets and poultry, you are going to have a higher proportion due to poultry. The more things you look at, the more possible sources, the less you are going to have from poultry. And that is a limitation on the study and that is a bias that you get in your estimates.

DR. HOLLINGER: Right. And I --

MR. CONDON: And that is something you haven't really -- I haven't seen mentioned here, the bias of these estimates yet.

DR. HOLLINGER: Okay. Well, there are some description of that in the risk assessment text itself. But in the university study, it is not that they only looked at two risks. They certainly looked at more risks.

But because they looked at a subset of the population that did not have certain exposures such as raw milk exposure or had not traveled, I believe that, you know, when you say there are biases, certainly the high level of risk in that population was due to their limited exposures.

And I think that the reason that that study was included was because we have a lot of uncertainty in what that actual estimate ought to be, a more precise estimate. And we saw that between -- somewhere between 48 and 70 percent we thought would be an estimate for -- or it would be a broad enough range to include maybe the actual estimate for the general population because the general population is certainly an average set of exposures.

MR. CONDON: Well, but there are a couple of issues. One is the -- you've got a study that in your report here -- and I have only had a chance to look at this briefly -- it says it is not representative. Okay. I think at that point when you are trying to make an inference back to the population, you take that study, you put at the top of it, "Sample not representative", you put it away. You don't worry about it. You don't get confused by trying to use it.

I mean, the best example I can think of as far as a nonrepresentative study is in 1936, a political poll was done for who was going to be President. One hundred thousand people were asked. Roosevelt was going to be overwhelmingly defeated was the results of the poll, not even close.

There was a question about the representativeness of the poll. It was a telephone survey. And if you think back in 1936, a lot of people did not have telephones. A lot of the people who did not have a very high income did not have telephones. So there was a bias in that. And that set polling back 30 years.

DR. HOLLINGER: I would say --

MR. CONDON: And so that is where -- once you say the data is not representative, put it away. Don't even try to use it.

DR. HOLLINGER: Wait. No, no, no. You know --

MR. CONDON: Because it is just going to confuse you.

DR. HOLLINGER: Okay. And what I said was it was representative of certain sub-groups in the population, Bob. And the reason it was included was because we knew that people were eating more chicken than they had in the past. We knew that exposures have probably changed since 1981. And we wanted to show that we had little confidence in one single point estimate. That's why. David, did you have something you wanted to say?

(Away from microphone.)

DR. VOSE: Well, I just wanted to reiterate exactly what you said because --

DR. LONG: Come up to the microphone, please.

DR. VOSE: I wanted to reiterate exactly what Kathy has just said. I think -- we are trying very hard to recognize where we have uncertainty. And I think if we had gone to this one study, if you like, that had one figure, I think that that would have been more of a failure than to have taken some -- two studies that were dissimilar and say, well, hell, it is going to be somewhere in there, probably somewhere between the two.

It is much better from our point of view to recognize that we don't know that very well so that we instigate discussions like this because if we picked one single estimate, it is almost certainly going to be wrong. Actually, where we are right now, we are almost certainly going to be right that it is somewhere in where we are.

And maybe we can argue, but later.

(Laughter.)

But -- and you are quite right. There is going to be a bias in there because we have got that higher prevalence. But this is a work in progress. As Dr. Sundlof said, it is a living document. And if this -- okay. Well, if I put in a single estimate, it wouldn't ever have appeared in that spider plot that you all saw. It wouldn't have appeared there as something that is flagged say, hey, we don't know a lot about that.

Because it is there, we are going to have a discussion. And maybe -- I hope it is because it is a very dominant parameter of the model. I hope that we are -- it is going to instigate some more research that will try to get a better estimate of what those values are. So I still -- from a modeling perspective, I prefer a strategy of modeling if you like. I prefer to put it in.

And you will notice it had a uniform distribution. Now, I don't know if any of you will ever read my book. There must be somebody. No? Oh, Louise, hurray.

(Laughter.)

Were you to read my book, you would see that I loath the uniform distribution. I hate it a lot. But -- and the only time I ever really use it is to make it stand up and to make people shout about it and say, hang on, that's not fair. You know, we've got to know something a little bit better than that. Hence this discussion.

So don't too much pick up the numbers. But certainly if you have some better data, then -- any of you, then, my goodness, we would be very willing to see it.

MS. BARTHOLOMEW: I can add that we have had this sort of discussion sort of internally about this, that we are not all that pleased with the 70 percent as being representative. But we didn't have other things in black and white. And there are ways, in fact, to incorporate expert opinion. We just didn't know whose expert opinion we wanted to incorporate there I guess.

(Laughter.)

MR. : Maybe I should sit down then. We agree that this is an important estimate. And it would be nice to know precisely what the proportion of <u>Campylobacter</u> cases in this country are attributed to each food commodity. And it would be nice to know how much is due to poultry and other foods.

I think it is in your range of estimates, the 48 percent to the 70 percent, is entirely defendable based upon the current published data. It has been replicated in the United States in smaller studies. And it has been demonstrated in very recent large case control studies in New Zealand, in Denmark and in the United Kingdom.

And whether you decide to put the -- use the uniform distribution, if you decide to put it at 48 percent or 70 percent, it doesn't -- the outcome is just influenced -- you still have this demonstrable outcome. And os if you want -- prefer to use a more conservative estimate, 48 percent or some people actually want to go lower than that, then you still can decrease the outcome by just as much.

But you still have this demonstrable outcome. So I really don't think it is -- it certainly -- to quibble about where to exactly put that estimate would be to speak against the current literature which has already gone through peer review.

MS. LASKEY: I am Tammy Laskey. I am an Epidemiologist at the Food Safety Inspection Service. And this may be a bit of a digression. But the contradiction of having a large proportion of cases associated with raw milk consumption and then such a low prevalence or exposure to raw milk in the population that one can't study it suggests that the probability of becoming infected given that the bacteria are in the raw milk is different than the probability of becoming infected if the bacteria are in the chicken for whatever reason, either a dose or a virulence or a strain, a reason that we don't know.

But it is a piece of very important information. And I would suggest it needs further exploration. It is very intriguing, as well.

DR. HOLLINGER: Well, I think the level of exposure from raw milk to chicken, the comparison, I mean, the difference is going to be huge. Very few people are drinking raw milk. And since I believe 1987, there was a raw milk interstate ban of sale. So raw milk has generally been associated with outbreaks. And that represents less than maybe one percent of all Campy cases.

So raw milk as far as being significant in this risk assessment is probably not. It is probably very, very small compared to poultry.

MS. LASKEY: Right. But I was saying in terms of understanding Campylobacter infections in general and the contribution by raw milk, it is suggesting something different is happening in the raw milk situation than -- because it is a way disproportionate number of cases. Even though it is small, one percent of the population does not drink raw milk. So finding one percent of the cases there is very strange. And I am just bringing this contradiction up as a point for further study.

DR. HOLLINGER: Thank you.

(Away from microphone.)

DR. VOSE: Kathy, does that have to do with the detection of milk before the infection ---

DR. HOLLINGER: I don't think that really, that if one percent of the population is having -- is an outbreak-associated case, fewer cases are raw milk-associated cases, much smaller number. As far as I think what she was getting at was somewhat about the pathogenesis.

And I think the interesting information that was brought to us from Canada about cross-contamination within the kitchen from poultry sources also is very interesting. So it really may be vehicle dependent. And, you know, the infection or susceptibility to infection may be vehicle dependent.

Certainly, Salmonella has shown that -- in fatty foods, that it is protected in the stomach from acid and then is more likely perhaps to cause an infection. So, yes, that is an area that could have more research done to understand. But, again, because it is such a low number of cases, that is a question apart from this risk assessment. Yes?

MS. MORNER: My name is Ann Morner. I work for Bayer in Europe. And I just wanted to draw your attention to Danish results within the Dane Map Surveillance System in which there is a considerably higher resistance level in Campylobacter isolated from retail products compared to isolates from the carcasses at the slaughterhouse indicating that something is happening.

Then I had a question regarding the -- if you have taken into consideration the number of people at risk, whatever 4,000 to 6,000 people being at risk, how many of these cannot be treated with fluoroquinolones because of their age or because of other factors so that they will not be given the fluoroquinolones as a first time choice.

DR. HOLLINGER: Yes. In response to your first question, the Dane Map and Danish situation, that difference has been demonstrated because of imported products. A lot of the imported foods -- and this was also demonstrated in the U.K. That the imported products has higher levels of resistance than did the domestically produced products. So that is one issue.

And as far as the children who were not treated with fluoroquinolones, we only looked at that actual proportion of people who were treated with fluoroquinolones. So those people who had other treatments or who were not treated were not considered in this risk assessment.

MS. MORNER: Thank you.

DR. KRISHINSKY: My name is Beth Krishinsky. I am with Wompler Foods. I just had a question on the volume of boneless, domestically-reared broiler that is consumed -- broiler products that is consumed in the United States.

With the changing trends and consumption patterns from cutting up a whole bird at home to eating pre-prepared breaded, fried fast food products in the general population, fast food restaurants, how do you reconcile the exposure to raw chicken as being a source of Campylobacter infection or cross-contamination when an increasing percentage of chicken that is consumed is already precooked and packaged either in a restaurant or in fast food?

DR. HOLLINGER: What can happen in that circumstance is that they can be preparing the food. But after the food is prepared, they can handle or contaminate it. So food handler education would be very important. And

I think that it is -- there is a considerable amount of cross-contamination either in restaurants or at homes. And that handling food isn't the only source of people's infections.

DR. KRISHINSKY: Do you think that your assumption of the volume of poultry that is consumed in the United States should be adjusted for products that are already pre-breaded and sold frozen and only deep fat fried at the restaurant site?

DR. HOLLINGER: David has an answer for that one. Excuse me.

DR. VOSE: You've got a good point. And one could do that. The value of K, this mystical K value, implicitly takes into account what you are saying. There is only a certain number that will go out into the consumer's pathway that still contains Campylobacter. And we don't know what that is. We have never tried to address it.

So there is a proportion, if you like, where you could separate that proportion that is already pre-cooked and never goes near a consumer before all the Campylobacter are dead and then that which are uncooked and received by the consumer.

And if we did that, we would say, well, the volume of meat now is much smaller. But the value of K will be correspondingly higher. It would quite amount to the same thing because we were saying that we now have a fewer number of pounds of potentially contaminateable meat. And yet they are producing this level of infection in humans. So this sort of --

(Away from microphone.)

DR. KRISHINSKY: ---.

DR. VOSE: Only if you see the chickens produce infections, well, absolutely right. I mean, of course. But if that is wrong, then, you know, the whole thing is blown out of the water. Yes.

(Laughter.)

But, absolutely. And I do hope that we make that assumption explicit. If we didn't, then I am making it now. If that is a shock to any of you, I hope not -- okay.

(Away from microphone.)

DR. KRISHINSKY: --- not agree with it.

DR. VOSE: Okay, well, if you don't agree with it, then yes.

DR. LONG: We need to move ahead. We will have one more question and any other comments can be deferred to the public comment section at the end.

MR. BRIAR: Yes, Mike Briar from Alfarma. I am having a little hard time figuring out just how this is going to fit in. But your number one assumption was that all of the resistance came from fluoroquinolone use in poultry. Am I correct about that?

DR. HOLLINGER: That is correct.

MR. BRIAR: And I think it is on page 313, you had a little footnote. And I assume that is based on this 1992 study that showed that there were no human isolates that were fluoroquinolone resistant.

DR. HOLLINGER: Right.

MR. BRIAR: I came across a paper that went from August 22nd, '92 to August 25, '95 which if memory serves me right was just before approval of serafloxicin in poultry from the Medical College of Wisconsin. And they had 12 percent resistance in their isolates as of the point just prior to the approval. I don't know how that figures in with your assumption that --

(Away from microphone.)

MR. : That was --- or that was ---?

MR. BRIAR: It doesn't say, but it is certainly not limited to --

DR. HOLLINGER: Right.

MS. : There is always that --- infections in travelers.

DR. HOLLINGER: We looked at domestically -- yes.

DR. BRIAR: It does not say anything about it.

DR. HOLLINGER: We looked at domestically acquired resistance. And our assumption was that everything was chicken-associated. And we removed the travelers and we removed prior fluoroquinolone use. And for those people who did not know or those cases for whom it wasn't known when they got fluoroquinolone.

As far as any prior fluoroquinolone resistance that was domestically acquired from food-borne sources in the United States, I am not aware of it from the data searches that we have done. But we would be very happy to have that paper and have a look at it and see if it changed --

MR. BRIAR: I don't know how this would figure in. I am just saying that it was rather striking that they did some rather extensive typing and they came up with 40 C. jejuni. And they had 12 percent of them already resistant prior to any use in food animals.

DR. HOLLINGER: We see this --

MR. BRIAR: It looks to me like in your model -- now, I may be wrong. Please correct me if I am. But it looks to me like your model that you would assume that any -- in other words, you are just taking the poultry percentage and applying that to the cases in the --

DR. HOLLINGER: What we did was we removed all the potential sources of resistance that would not be acquired from domestic sources. I believe in Canada also there is a hospital study where they show resistance in people and maybe someone here from Canada can speak up. But they do not use fluoroquinolones in food animals either. But a lot of these infections can be acquired from travelers returning from trips to places where they use fluoroquinolones in food animals.

MR. BRIAR: You know, it doesn't say in the paper, you know, whether that was travel-associated or not. It simply said that they had, you know, the 40 -- actually, there were quite a few more isolates, but 40 C. jejuni. And that was a little bit higher even than what we see from the NARMS data in poultry. That is what struck my --

DR. HOLLINGER: So, you know, this is a call for information. So please, you know, submit it. I would be very happy to look at it. Thank you.

PANEL DISCUSSION ON CVM RA MODEL

Dr. Wesley Long

DR. LONG: Okay. Great. We are going to move on now. I would like for the panel members to come up. And I am going to talk about the rules for the panel discussion as they come to the stage.

We have had some really interesting information today. We have had the risk assessment presented to us. We have had a lot of really good questions that I am sure that CVM -- well, I think they have probably thought about most of these things and debated some of these things. It just shows that we have an intelligent audience that is able to draw out these issues that clearly may need further consideration.

The format for this panel discussion actually allows each panel member, I am going to give them about eight minutes to go through the seven questions that are posed that are on everyone's agenda under "Panel Discussion on CVM Risk Assessment Model."

After each person gets a turn to address those seven questions -- and let me just tell the panel members that you can just go through and tick them off. And that is what I am going to do and I am going to be very brief and I get to go first.

You can choose one of those points that is most important to you that you think really needs to be addressed. If you want to go outside of the questions, as well, you have that option. But I will be running the time clock and it will be right up here. And if you could keep your eye on it when it is your turn, we need to ensure that we stick within the time frame.

Following this then, there will be an opportunity for the public to address questions to the panel. Following that will be a public comment period for comments for the public. So with that, I am going to sit down and take my turn.

MS. : Wes?

DR. LONG: Yes?

MS. : Could you have them turn the lights on in our part?

DR. LONG: You bet.

MS. : Here in the back.

DR. LONG: I forgot to say that there are a few people here who have get to be introduced. So as it becomes their turn, I will go ahead and pick them off. Most of these people have been introduced as being prior speakers today.

Okay. My preference is just to tick off through these questions in a fairly quick fashion and give fairly simplistic answers to each one. The first question, what are the positive aspects of the model. And not to be facetious, but I think one of the great positive aspects is that it is done and it is out in the public and it is here to simulate -- stimulate -- not simulate, we are done simulating for right now -- to stimulate discussion amongst all of you, amongst risk assessment peers and scientists, and to try to get -- you know, it adds to the limited pool of these types of assessments that we have on these types of products.

I personally don't have trouble with the assumptions that were made. And I will get back to that as

I work my way down the list. I forgot to start the clock on myself.

Okay. Limitations of the model, I guess, you know, this model is not going to ever be everything to everyone. And certainly the model does its best to address the question that was put before the risk assessors and certain it is what I think was necessary for CVM to move forward.

So as we saw in the examples, we saw some pathway analysis models, we saw a qualitative risk assessment model. Dr. McEwen showed us some pathway-related type modeling which I think is very useful and plays a role. But it wasn't the subject of this exercise.

In terms of significant data gaps, I will take the easy way out and say that Kathy Hollinger seemed to have covered them pretty well. And, yes, there are data gaps. But, no, I don't think those data gaps are of -- certainly, we can fill in the FoodNet data over time. We can collect better information and data. But I don't think it should stop us from using this assessment.

What aspects would I consider changing, I think I am going to defer on that question. Can this model be used to help CVM or the industry reduce the level of risk, that is sort of a -- you can answer that question in a lot of different ways. I guess directly, it is not going to help industry reduce the risk.

There is no mention of interventions that you can use to control the levels. There is -- it is not intended to be a recipe or a HACCP-type thing for you to insert controls in the appropriate point to achieve an appropriate level of reduction.

But what it does do is it gives CVM now the tool to work on this risk management decision which I think is really where the next step is in this process, that we now have a an estimate of the risk to human health. And, you know, as I listened to the comments today, this -- and as David said, somewhere within his range he has got the right number.

And I think I agree with him. But I think that fine-tuning that is always going to be a goal that we will have and we will continue to re-evaluate. But it shouldn't stop us from moving forward.

Should CVM evaluate other antimicrobial-pathogen combinations, I think absolutely they should. You know, the reason they told us they chose this one is because they had the best data. And, of course, that is critical to the assessment. But in terms of a comparative risk assessment so that they can prioritize their resources the best, I -- because I am not in the veterinary field, I don't know if Campy and fluoroquinolones are the number one issue or if perhaps it is another organism-drug combination.

And as far as alternative approaches, I think that this farm-to-fork approach which we have heard talked about a number of times today is a valid follow-up to this. And I think that it is going to require significant industry involvement to take on a farm-to-fork approach. And perhaps industry should take the lead in that type of approach. And that is my answer to the seven questions.

Paula is up next. And I don't think Paula got introduced properly. Did you before?

DR. FEDORKA-CRAY: Yes.

DR. LONG: Okay. Take it away.

DR. FEDORKA-CRAY: Do I need an introduction?

DR. LONG: You need no introduction. Here you go.

Dr. Paula Fedorka-Cray

DR. PAULA FEDORKA-CRAY: I will take Wes' extra four minutes. I think there are positive aspects to the model. And I will go with 1 and 2 and what do I see as the limitations of the model. And I think the answer to both is probably the research gaps. The positive aspect is is it identifies the research gaps that we can all focus on now to make better assessments as time goes on.

And I think that because we have an idea of some of the thought processes that have been identified here, that we will think about future risk assessments in a different way and begin to gather information. And I will address that as we go further on.

I also think that there was an assumption made that fluoroquinolone use in poultry is going to result in an adverse human health impact. And that is probably one of the largest and the most contentious issue here that we can have from both sides.

And I think that if you look at it from different perspectives and if we all step back and perhaps look at it in a more objective way, that we can see that really those questions -- that question could probably be answered in a number of different ways. And I think that we are all calling upon ourselves though to provide as much information as we possibly can to make the correct assessment as time is going on.

In my opinion, not only for job security -- I always say that, but it always comes more and more evident. But there are some significant data gaps that have been addressed. One of the things that I am particularly struck with is that obviously I missed it in the literature that humans -- someone said that humans can't become reinfected with Campylobacter. And I think my body missed that lesson at some point in time.

And that brings to mind one of the most intriguing questions, at least in my limited capacity up here, is to think that we are in fact exposing ourselves to multiple isolates that results in increased disease so that we may be immune to one different type of isolate that keeps changing over time.

This may lead then to the tremendous genetic diversity that a lot of people will talk about in the Campylobacter species and really confounds what we may be able to do in the long term then if we can't control that in some other way. And so from a research aspect, that may require us to look at this question very differently than we have in the past.

And it also suggests that there may be increased stresses in our immune system so that while we are busy containing one particular isolate that may be more virulent, other isolates have the potential to take over and cause the disease that we may then see. And this may be way we have this disparity between coli and jejuni.

The other thing that I think that I brought out was the difference in culture methodologies and the selection of isolates over time and how that may change, how that is different. I mean, one of the things that we are addressing is how it is different on the farm versus the slaughter plant versus retail. And I think those will become very critical issues at some point in time.

And I think that we really can't discount an environmental impact. Because of the global nature and the ubiquity of this organism itself, that really if we have already tipped the balance and if we already have an environment that is saturated with some type of bacteria, that there may only be X amount that we can do to, in fact, lower the graph, if you will. And then that begs again for interruption of the system in different ways.

I think that we are gaining some evidence that there is going to be increased -- that with increased resistance, there is an increased likelihood of colonization with prolonged shedding. And that is a virulence that speaks to pathogenesis. And I think that we have to go and we have to look along those lines.

I am wondering if we can't just do something very simple by suggesting that if we know that there was fluoroquinolone use on any farm at any one particular time, if they can't be slaughtered last in the queue in a slaughter facility and see how that may or may not affect what goes on in a processing situation.

And maybe that is not totally feasible and there are all kinds of implications for that. But that speaks to somewhat the Danish system with the Salmonella and slaughtering animals last after they have a known serologic change.

One of the things that has nothing to do with research but is a way that all of you can probably influence the process is we tend to only publish positive results. If we see something, we publish it. Well, what about the negative results? You know, what about the times that we know there is no impact whatsoever and it really never gets out there because a journal only wants to publish positive results?

And so we have this gap then and people saying, you know, you have to go to a meeting and actually ask a lot of questions and then have them say, "Oh, no, well, we've done that. Don't bother going there", or something. And so it would require tremendous change on a lot of different levels to actually have information published that would suggest that, in fact, something that wasn't observed is just as important as something that could be observed.

And then one of the things I think that we should do is look at -- in fact, look more closely at the role of Campy coli and some of the other Campylobacters and see if we haven't missed something. And bacteria have a unique way of out-foxing us no matter what we think.

And I think that if we look at the number of papers and information that has been published over time, that because we haven't really solved any one problem in its entirety as far as bacterial species go, I think that it speaks that we always need to look at things differently if we keep coming up with the same answer which is, "I don't know why this is happening."

And then one of the things that I think it might -- we might beg to ask is how many people have had repeat infections and what probability that is over time. And if we could look at a small number of people and look at the isolates that they may be shedding, that may give us some idea of what has happened to this population dynamics.

What aspects of the model would I consider changing? I am always intrigued by having one risk creating a second risk and if there is a probability of that. So that if you take away the use of, say, an antimicrobic at some level, do we create a second risk by allowing for an increase in some disease, whether it be bacterial or viral, and then where that will ultimately lead with exposure to an effect on public health.

And I think that that is something that we should at least consider because we are trending new ground here. And we really don't have a good answer for that. And I think we would be remiss if we didn't at least think about it. Maybe you are thinking that's plenty; we've thought about it enough. But I think it is something we should think about.

Can this model be used to help CVM or the industry reduce the level of risk? I think any time you have information, that can be useful. And if we are all walking away, there is always something positive. My mother has always told me there is a positive aspect to everything in life. So I think we should -- I will tell my mom that it works this way, too.

How should CVM evaluate other antimicrobial-pathogen combinations? I think it would be -- I think that I don't really know the answer to that. I think it would be good to have other risk assessments done. One thing that would be nice would be to have enough of a lead time and enough of an idea perhaps of what may or may not be going on so that the submission of data can come from a large number of sources that may be able to provide additional information that can be used in the risk assessment model.

We all have access to information and data that other people may not have whether that be published or unpublished works. And I think that having the opportunity to provide that, whether it ends up being used or not, is not a final call. But I think having the opportunity to provide it provides for more interactive processes and may also provide for more useful information.

And I also think that in some ways if it wasn't cost prohibitive that it would be nice to see a model done where we already know a lot of the data and we have a very, very good idea of what the expected outcome is going to be.

I just -- you know, numbers and calculators and punching things in are all very nice.

But I think there would be some merit to seeing something like that and that it would give a much higher level of confidence in the thought process in seeing how everything is going on with the bacterial-drug combination. I know that there are other risk assessments that have been done. But we are looking at something more specific here.

And an alternative to risk assessment approaches that CVM should consider, I don't necessarily know now that we have gotten into it that anyone is ever going to get out of this. And I think it becomes the new rage and the thing to do. It's like Pokemon. And, you know, we have Pokemon now and we have risk assessments now. And we will be going on to some other things, too.

But I really do think that we should not lose sight of the fact that what we are really talking about here is reducing pathogens. If we reduce pathogens, then it follows -- at least in my assessment, it would follow that we reduce the percentage of resistant pathogens, too, or that would be a good starting point.

And I think that we have to keep sight of that fact and we have to keep working toward the goal of, in fact, reducing those types of pathogens regardless of whether they are resistant or not. And prudent use becomes absolutely critical in this for all of our constituents.

And then I think that we really have to look at implementation of alternatives. Since the issue isn't going to go away and if some of these other assumptions are true, then this begs -- we can develop a vaccine. If immunity happens once, I would be over -- all -- you know, that low dose, avirulent, get it over with one day. You know, it is like a flu shot. And then, of course, probiotics and other issues, too.

And I think that we really have to look at the implementation, actually put them into practice now and see if we can use something else while we are trying to fix this issue, too. Thanks.

DR. LONG: Scott?

Dr. Scott McEwen

DR. McEWEN: Yes, you already heard from me, so I won't sort of reiterate too much stuff. I think -- what are the positive aspects of the model, I think first and foremost has been said. It is done. It looks to me like an excellent job, so compliments to the group on the whole sort of process. Again, I underscore that we have the model. In fact, there is a public meeting on it and there is wide-ranging discussion and there is people from all different fields that can sort of take punches on it and add to it. I think that is terrific.

I think it is very important that regulatory agencies with the kind of stature of FDA does this kind of thing because I think that sends out a great signal to a lot of other places. You know, sitting at a university, I think this is going to have reverberations in our graduate training program and of people that are going to have to develop the skills to sort of get involved in this kind of thing which I think is excellent.

Lester mentioned that the teaching value of this sort of exercise. So it has I think a lot more impact than the specific topic and issue, Campylobacter and fluoroquinolone resistance, though I think a lot of people in the room would probably -- we all have our own interests and I think that is a major one for me.

I think the -- another positive aspect that hasn't really come out is my understanding is that in a lot of public applications of risk assessment, if there is uncertainty and default assumptions are made, those are usually to favor public health. And there is good reasons for doing that.

If we don't really know how it is working, then sometimes we make worse case assumption. And then the onus is on other people to go out and get more data to show that that is not the case and we should redefine that.

I think FDA seems to have done a good job of balancing that, not sort of gone overboard on that particular aspect I think is a positive thing. And as people have said, the explicit assumption description, sensitivity analysis, I think all that -- transparency although I don't like the word, I think that inspires a lot of confidence in the process and helps with growth and people understanding it and that kind of thing. So I think -- and there are other positive aspects, as well.

What are the limitations? Again, we talked about the what I would say ecologic nature. There is probably a better word for it than that. And I think that -- although I understand why it was set up that way and I think there are good reasons for it, I think I would sort of like to see the effects of maybe refining some of the parameter. I am not an expert in sort of parameter estimation.

But just as one example, there was the -- we saw in Dave's literature how the effect that the -- the prevalence of fluoroquinolone resistance in slaughterhouse isolates had, how important that was. And yet I think as I kind of read it, it looked like what the -- the way the data were collected suggested that the standard errors might be under-estimated based on the sort of possibility of clustering at sort of slaughterhouse levels.

And, again, I don't really know. I suspect, as Dr. Cox said, that some of these things don't have much impact on the sort of outcome, but it would be good to sort of evaluate that.

I think the assumption that an infected -- person infected with a resistant organism in his treatment -- corresponds to the treatment failures, well, a reasonable one I guess I wonder about that. And I would like to hear about clinical experience in that area.

Do you feel there were significant data gaps, I think everybody would like to see more direct evidence if you want to call it that or evidence of drug use in these animal populations and resistant selection and so on. I think we need more of that. Whether it takes the form of this kind of assessment, I don't know. It could be -- there are lots of other approaches to addressing that as I said.

What aspects would you consider changing, one thing I don't know a lot about but I am interested in is separating out the variability and uncertainty components. I think we sort of talk about those things as equivalent. And in some cases, there are pragmatic reasons for doing that. But I think it would be good for people to have an idea of how much of the influence on the outcome is due to how uncertain the parameters are versus their variability biologically and other ways.

Can this model be used to help CVM and other industries to reduce risk, yes. If it is -- and as I see it, it hasn't yet been used to look at the effects of interventions and test hypotheses. But I think that would be a great thing to do.

I guess we -- to be strictly speaking, as Steve said, you have to define what is an acceptable level of risk. And that hasn't been defined yet. So you could make the argument that the level of disease out there is acceptable. I personally don't believe that, but that could be stated. In that case, then there is -- under that scenario, there might not be a need to reduce risk. But, again, I think that is not true.

As always, I would like to see some economic assessments used in conjunction with evaluating different risk management strategies to see what kind of collateral damage might be done, if you will, in other industries and sort of weigh that in the equation somehow.

How should CVM evaluate other antimicrobial-pathogen combination? Again, I ran out of time, had too many slides and had some there to sort of reinforce what Louise was talking about on the qualitative assessments. I think that given the large number of pathogen-drug combinations, I think it is unlikely we will be doing full blown quantitative assessments on all of them.

And I think -- quantitative that is. And so I think qualitative assessments are going to be important.

And we need to have better ways of doing that, more structured ways of doing it. And I think that will move along.

I think, again, that there is a merit in having what we called in a previous talk a tiered approach to this. We have a sort of screening level of qualitative assessment. It looks like there is no problem. We don't need to go any further. And as the ante is up for a variety of public health or cost reasons, then we could start to engage in more quantitative assessments.

And I believe that has worked in other fields. I think it could work here, as well. I think we have to move into ways of assessing the quality of information, scientific information that the GENACAR Report from Australia gets into this quite a bit. The weight of evidence approach I guess, the evidence-based medicine approach of somehow weighing how well a study was done, how representative it is. And I get a sense of how believable it is into the equation. So with that, I will pass on to Louise.

Dr. Louise Kelly

DR. KELLY: I think I need a cushion this time. I can't sit on there. It is too uncomfortable. Anyway, well, to start off, what are the positive aspects? Well, just for David and my best Glasgowegian accent, I think it is pure dead brilliant. I really do. I think it is a great attempt at considering this problem that we have been looking at ourselves in the Veterinary Laboratories Agency.

And it is not an easy task. It is a difficult -- risk assessment, development of these models is not simple. A lot of people think that it is. It is a difficult task. And I think you have done a really great job.

And all the way through reading this report, I think it has been completely transparent. Everything has been laid out. All the assumptions are laid out. And from this, we could then if you want to take it back and try and reproduce the results yourself.

And I think the transparency is always put down as one of the most important, crucial elements of a good risk assessment. And I think this falls through throughout the whole report.

In addition to this, I feel that there has been a real team effort involved in the development of this model. It has been multi-disciplined really. It is not just a mathematician who is sitting in an office developing the model. There has been input from every possible background. And, again, I think that is very important. So I really do think this model has a lot of positive aspects.

The limitations of the model I think really depends on what perspective you are coming from and what particular question you are trying to address. And in this aspect, I think the model has addressed the question it was asked to address. And it has done that very well. So from that point of view, I really don't see that there are many limitations.

Obviously, if we were considering estimating this risk from another perspective, for example, considering control on the farm level, then that would be a different risk question that we would be trying to address and a different type of model would be required for that type of problem.

So really it comes down to defining your question in the first instance. And that has been done here and followed through. And I think, therefore, for that particular question, the limitations are really limited in themselves.

Significant data gaps, well, it has been acknowledged that there are data gaps within this risk assessment. But they have been laid out in the report and they have been accounted for by adequate uncertainty assumptions. And I think I am right in saying that the separation of variability and uncertainty has been undertaking in the model to a large extent.

I think you are nodding, David? Yes. Because essentially what the final outcome for Stage 3 was nominal expected value. And that itself is described by a variability distribution Poisson process. So that has been accounted for.

Aspects of the model that I would consider changing, none really, again, for this particular question. But, again, depending on a different perspective and a different type of question, maybe a different approach would have to be accounted for.

And, again, as Scott mentioned, I think the idea of integrating risk assessment models with economic analysis is a very good idea because these drugs do have benefits both to the animal and to the human. And we have to consider that. To a benefit-cost analysis, benefit-risk analysis if you like would be another good way to go.

Can this model be used to help manage the risk? Well, I think that we have to remember that risk assessment models, and this one included, are dynamic tools and they are tools. The aim is not to concentrate on the final numbers that come out of these models. They have to be appreciated as being tools which need to be updated as new information becomes available.

And the estimates that come out of this model are really based on 1998 data which can be updated. And, therefore, it is dynamic and can respond to monitoring information which needs to be undertaken at the same time.

So I think it can be used as a regulatory tool.

Other antimicrobial-pathogen combinations, yes, I think that that should be undertaken. But I think we have to pay cross-consideration to the type of modeling approach that we might need to use for these different combinations. It would be a danger to consider that this model developed from Campylobacter and fluoroquinolones could be used for any other species and drug combinations.

Each problem, each combination in this way has different aspects, different processes that need to be considered. And, therefore, the thought process has to begin again for the different combinations. So we need to remember that we can't just simply present new figures for new bugs and for new drug combinations. We need to think again about the whole process.

And the alternative risk approaches, well, we presented today -- well, I presented today our farm-to-fork type approach. That is another method that can be used. But, again, we have to consider what exact risk question we are trying to address and really the available data that we can use to fit within a model. And it all depends on the problem that we are trying to consider for our risk assessment. And with that, I will now step down again.

(Laughter.)

DR. LONG: Steve?

Dr. Steve Anderson

DR. ANDERSON: All right. Well, I think -- first of all, I think the CVM team needs to be congratulated, as well, because I think it is a very good product that they have generated. They have used the sort of quantitative methodology and they have supplied the actual spreadsheet which I think is great because, again, I will echo everybody else's sentiments, is that we now have the spreadsheet.

And you can take that. And it provides that transparency. You can take that and work with that on your own and see how you agree with the model, as well. So I think there is the transparency component that is an excellent part of it.

The model makes full and complete use of the available data. The surveillance data and the monitoring data and the CDC data, it kind of brings all of those things together and ties those together very well.

The study also recognizes the uncertainty. And I think that is a reasonable thing, especially when the risk managers take this and start working with the actual risk assessment product. It will be a good -- good to recognize that there is uncertainty in the values generated.

The limitations that I would say that I see are I would like to see probably the pathogen load or the concentration on the carcass considered. And I think that is really important. In our model, we can take pathogen load, hold it constant and raise the prevalence. And you will get an increase in the incidence of disease or illness.

The same thing, you can hold prevalence constant, raise the concentration or the pathogen load by the same amount, and you will get similarly increases in the number of illnesses. So I think those two things actually work together. I don't think you should actually exclude one or the other. And I also think those to things, the pathogen load and the prevalence, they kind of work together in that ultimate dose.

The other problem or limitation that I see is in the market data was used to give the final consumption amount of poultry which was 50 some-odd pounds. And I think that you could use the consumer survey for food intake data set or the NHANES data set that actually tracks consumption patterns and get a little bit better handle on the actual consumption data because market data is going to over-estimate what people consume because that includes wastage as well as what is actually consumed. So actual consumption data is what is really needed.

The other limitation I see is it doesn't really provide many options since it is such a simple model for interventions. And the ultimate intervention it seems that I can think of would be controlling or banning the use of the product. So having a more complex model may be more difficult. But you also have the increasing opportunities to -- for mitigations and suggesting mitigations.

The data gaps I think have been covered adequate. The things that I would consider changing, again, I would really strongly urge that sort of the concentration or the pathogen load be added. And that can be derived from the USDA baseline data where the prevalence of Campylobacter was originally derived on the carcass. Again, I would use the consumer data, as well.

And then the next question was can this model be used to help CVM or industry reduce the level of risk. And I would say it is a good start. I would suggest maybe another year of data. But we are already at the end of '99. So I presume that the '99 data can be entered into it, as well. And then I think it is a useful tool. I think it is a simple model. But that may be the nice thing about it. It contributes to the understanding of how those figures were derived.

Now, how should CVM evaluate other pathogen and antimicrobial combinations, and I think that is a case-by-case basis. I think in future risk assessments, you need to consider other sort of pathogen-specific things like growth and how the drug is administered. In poultry, it may be administered quite differently, in water. In cattle, it may be injected. Those are significant. How the resistance is acquired and spread also is important.

I think of this as more of a horizontal risk assessment in many ways because it is a very simple model. And perhaps doing a more farm-to-fork process model -- process-based model might be useful.

Alternative risk assessment approaches, again, would be a farm-to-fork model. The other possibility is the Canadians are also finishing a Campylobacter risk assessment study. And I think you could put the resistance data into -- and the resistance trends into that risk assessment and also sort of better derive what the relationship is between the animal prevalence of resistance and then how that relates to the incidence of fluoroquinolone-resistant illness. And I will stop there.

DR. LONG: Thanks, Steve. Dr. Lipsitch is next. He is Assistant Professor of Epidemiology at the Harvard School of Public Health -- oh?

DR. LIPSITCH: Randy is in between us. I don't --

DR. SINGER: It doesn't matter.

DR. LIPSITCH: I have some slides. So I can put them on while you --

DR. LONG: Oh, okay. Randy is up next, okay. Well, Randy, even though the program -- or even though his badge says he is in California is -- maybe he wishes he was in California at this time of year. But he is Assistant Professor of Epidemiology at University of Illinois at Champagne-Urbana.

Dr. Randy Singer

DR. SINGER: Okay. Well, I would like to thank CVM for inviting me to participate. Rather than walking through this list of points, I see a lot of them as interrelated. So I would like to discuss the relevant points, you know, together.

Well, first there is the question of what are the positive aspects. And I think that does play directly into what are the negative aspects. The positive aspects, like has been said, is that the process is started. And, you know, this is a great first start at -- it has outlined some important areas for further research.

But it plays directly into what is really in my mind an important negative that we need to be careful about. And that is to reiterate something that Doug Powell said this morning about risk communication. I really truly believe that the public does not understand risk. They don't understand probabilities. But when they know that FDA, CVM and a group of experts are talking about a risk assessment model, they are going to hear the words, "chicken", "antimicrobial resistance", "resistant bacteria", and "risk."

They are not going to ask, "What is my risk or what is the probability?" They just hear the buzzwords. And to them, a product gets singled out as a risky product, especially with the media play today that we see with antimicrobial products.

So the risk communication aspect doesn't take place just between us. It doesn't take place when the model is finished. I think there is going to need to be some careful consideration of how just our convening here is related to the public and so that an unfair negative impact isn't seen in a singled-out industry.

The next I guess questions that interrelate are how to use this model and what are some of the data gaps. I see some of these coming together. Well, one of the purpose of designing a risk model -- one of the tools is a hypothesis-generating tool. Another might be that it outlines key areas where we need more data. It might help us establish some thresholds.

But one of the key ideas in my read of this model is we want to outline -- well, that is quick. That's all I get because I am an assistant professor.

(Laughter.)

DR. LONG: Go ahead. Finish.

DR. SINGER: In the -- in a risk assessment model, you often want to identify foci for risk reduction strategies. And I understand that this is at the point of being called a simple model.

In reading through it, at the very end of Section 5 if you all had a chance to make it that far, there is this variable thrown out called Pmax which is defined as the maximum acceptable prevalence of fluoroquinolone-resistant Campylobacter on chickens. And it is suggested that this might be the threshold that we set.

Perhaps in a processing plant, if Pmax is overshot, then something has to happen. Maybe fluoroquinolones are pulled or something. So this is a possible risk reduction site. The concern I have is that many broiler producers currently don't use fluoroquinolones. So if you are in their processing plant you find that they have overshot this Pmax, well, then what do we do?

And that brings up in my mind kind of a disconnect of the model. Where we want to invoke a risk reduction strategy is at the farm level. We are not interested in telling people when they get to the people -- well, maybe we are, but what antibiotic they should receive or -- we are more concerned about how do we manage it on the farm. And yet the farm component is completely absent from the model.

So while I do understand that it was meant at this point to look at the risk through consumption, to me if it is really going to have the risk of risk reduction, we need to include the farm component and get a better understanding of the relationship between fluoroquinolone usage, the development of fluoroquinolone resistance and then that transfer mechanism as it might occur to humans.

So that addresses this data gap. And then how might we manage it? At this point, I don't see the model as being so useful except in identifying key areas where we need to collect more data.

Another issue I would like to bring up -- and this is maybe being an epidemiologist, thinking of causal inference all the time -- is how we need to really be careful how we assume the causal nature. Some have said today that we aren't assuming any causality. And some have said, well, we are definitely assuming causality. We are assuming that the fluoroquinolone resistance we see in chickens, that was Campylobacter, are the fluoroquinolone-resistant Campylobacter that we see in humans.

So we are not -- we don't seem to all agree on whether or not this is a causal connection. The problem I have is with the methods that we might even use to assess causality. I have been looking recently at some of these molecular epidemiologic techniques from their actual methodologic aspect; I mean, how we actually use them.

And what you find is this difficult situation where if two isolates are different, then they are probably different. But if the isolates have the same fingerprint, what can you say? It would be nice to say that they are identical and so that is the source. But one of the other explanations is that you just don't have enough resolution.

To pull out in my read of the New England Journal of Medicine study from Minnesota, while, yes, they found identical DNA fingerprints in the Campylobacter -- in the resistant Campylobacter in humans and the resistant Campylobacter on domestic chickens, they also found some of those same fingerprints in the resistant fingerprints from internationally acquired infections.

So if we can't even -- we don't have the resolution to do a trace-back within our own country for domestically acquired cases, I think it is difficult to assign this causal link. And I am just trying to -- again, it is -- it needs to be done cautiously so that we don't incriminate any single producer or single industry, etcetera. How much time do I have?

DR. LONG: I'll give you two more minutes.

DR. SINGER: Okay. Well, one of the other concerns I have -- and maybe this is just my own personal thing. Maybe most of the other statisticians, mathematicians here wouldn't agree, is that in my background of a Bayesian analysis, the purpose of that prior probability is to take into account the expert opinion, to take into account our uncertainty coming into the problem.

But the way this model has been written is that every prior distribution was modeled as a uniform 0-1 which converts to a beta 1-1 which for those of you who don't know anything about probability distributions means that it has very little weight. So if there is a lot of data that were collected, those get weighted very heavily and the prior means nothing.

So what that means is that the entire uncertainty in the model in my mind is coming from a statistical uncertainty generated by that beta distribution. It does not allow us to account for biological uncertainty, nor does it allow us to account for differences between the various studies that were interconnected in this model.

In a meta-analysis which is typically where you would take many different studies and try to reach some end product, you account for the different study designs by weighing them differently and by adding uncertainty factors.

And so my concern is that we haven't done enough -- it might not ultimately make a difference at all in these probabilities. But without yet having had a chance to really go through the model in detail, I am concerned that there isn't enough uncertainty in the model inputs.

And so the comment was made that they were impressed that there is very little uncertainty in the model outputs. And that to me says that, well, that's obvious. There might not have been enough uncertainty in the model inputs. So I would -- as we continue to develop this process would just like to explore more the use of expert opinion and uncertainty into the model.

DR. LONG: Thank you. Okay. Where did he go? There he is. Okay. Now, this is Mark Lipstich -- is that right?

DR. LIPSITCH: Lipsitch.

DR. LONG: Lipsitch. He is Assistant Professor of Epidemiology at Harvard School of Public Health. And his research uses mathematical models to study the transmission dynamics of infectious diseases.

Dr. Mark Lipsitch

DR. LIPSITCH: Thank you. Thanks for the invitation to come here. I have a few comments that are on sort of various topics. I think they are responsive to the questions, but I haven't really tried to key them to the questions.

(Slide.)

So I will briefly talk about the strengths of the model as I see them. And then talk a little about the limitations and then the question of setting thresholds and responding.

(Slide.)

I would like to start by commending FDA on the -- I am not going to -- and Dr. Vose on really a very impressive model. And I think if anything, the concern is that we may be spoiled by having such a nice model for a system where there is so much data. I mean there are certainly significant gaps.

But I think my strongest point today is going to be that we can't know everything and that this may, in fact, be really as good as we are going to do for any pathogen that might be of interest. Having said that, I have four brief comments about limitations of the model.

(Slide.)

The first of those is that the report makes very specific predictions about the number of excess fluoroquinolone-resistant Campylobacter cases, the result from use of fluoroquinolones in chickens. What is not totally clear is the toll of these additional infections on human health and welfare, although there was some discussion of that today in terms of additional days of disease.

It would be possible to make such estimates using those sorts of data on differences in the duration of disease. And it would also be important to consider separately the impact of resistance and potential treatment failure on the rare or a bit more severe cases of invasive disease.

And finally, also to consider the effect of resistance on the duration of symptoms in untreated patients, as there has been some suggestion that even in the absence of treatment, resistant isolates may cause worse disease. And the last point here is we might want to know how these effects are different in different sub-groups of the U.S. population that might be at elevated risk such as immunocompromised people.

(Slide.)

The second limitation is that the model is really a static model. And the flip side of that is it is an easily updated model. So -- but I think it will be important to consider how these estimates are changing over time as the number of resistant isolates possibly increases. And we heard discussion earlier from the Minnesota data that the prevalence of resistance in Campylobacter appears to be increasing already this year over last.

(Slide.)

The third point is on the pathogen burden which has been mentioned a little bit today. But I think it is important to emphasize that the model assumes that the human health impact of fluoroquinolone use in chickens is the increased likelihood of exposure to resistant Campylobacter. But it doesn't consider another issue which is mainly the effect of fluoroquinolones on pathogen load.

So if, for example, fluoroquinolone use substantially increased the load of Campylobacter or other pathogens in chickens, then that would increase the risk of Campylobacteriosis or other disease for an individual consuming that chicken. And that would be an additional impact that just isn't factored into the model, but which could be I think fairly easily obtained if one had data on changes in pathogen load following treatment.

(Slide.)

And the last point of the limitations that I want to make is it is very important to remember that although the harms of Campylobacter are probably the most readily quantified, they are not the only ones. And they may not be even the most important human health consequences of fluoroquinolone use. And this is not so much a limitation of the risk assessment as a concern that it should be viewed in the proper context.

And this goes back to what I was saying about not being spoiled by the high quality of the data on this topic. Non-typhoidal Salmonella infections, for example, account for almost ten percent of food-borne illnesses, less than Campylobacter. But one-quarter of all hospitalizations for food-borne pathogens and almost a third of all deaths, about 553 per year in this country according to the CDC, and that is more than five times the number caused by Campylobacter.

And high level fluoroquinolone resistance remains rare in food-borne Salmonella in this country, but lower susceptibility reflected in increased MICs is being observed in Salmonella in the U.S. and other countries that use fluoroquinolones in poultry. And this trend appears to be worsening.

These Salmonella with reduced susceptibility are frequently only one mutation away from full resistance to quinolones and that makes them an ideal substrate for the development of higher level resistance, either upon further veterinary exposure or in humans who are treated.

(Slide.)

Now, scenarios like that are undoubtedly harder to quantify precisely than the immediate problem of resistance in Campylobacter. And it was very sensible to start with what is most easily quantified. However, we know that each of those steps in the scenarios is possible and that once fully resistant Salmonella appear in our flocks, it may be at a considerable selective advantage, although that is an area where we certainly need more data.

The fact that we don't yet have a noticeable clinical problem shouldn't make us conclude that we can wait until the clinical problem because obvious. And I put up this data from vancomycin-resistant enterococcus just to make the point that I think there is a relevant parallel.

If you look at enterococcal use -- sorry, vancomycin use in human medicine starting from the '70s, you had almost -- well, well over a decade of use of the agent before resistance became a problem. And that may be sort of like the stage of which we are now in, something like Salmonella.

But what is important to see is that once it appeared, it increased very, very rapidly. And it has been hard to get rid of. And so my point here is simply that this is not the same pathogen. There are a lot of potential differences. But that focusing on where there is a big problem and a quantifiable problem shouldn't distract us from what could be later on a greater problem.

(Slide.)

So, finally, I want to comment on the question of how risks can be reduced and in particular, on what might be done if the level of risk were judged to have reached a level that is unacceptable, that Pmax I believe. I must say that having read the section of the draft report on establishing regulatory thresholds four or five times, I still don't understand the solution that is being proposed.

But I think that what is being proposed is that when a level of human health impact is judged unacceptable, the Agency would take some mitigating action which I suppose would mean restricting some use of fluoroquinolones. And the problem with that approach is that resistance is not something that can be simply switched off by curtailing the use of a drug. And this is the point that Dr. McEwen made a little earlier.

Once we reach a level of human health impact that is judged unacceptable in either -- in any pathogen, even if we recognize it right away and take very strong action, we might continue to have the resistance problem for some years following that intervention.

As far as I know, there are no data that addresses what happens in Campylobacter following a reduction in use of fluoroquinolones. But we have some reasonable parallels in -- potential parallels in human infections. And I just wanted to show one example from what is really universally the success story that everyone cites for why we should reduce antibiotic use in human infections.

(Slide.)

And the orange line shows the reduction in erythromycin use in Finland from a level of three, about a six-fold reduction. And while this is cited as a great success story, what you see is that following that reduction, we have several years of continuing increase in resistance and then a decrease. And the decrease was about two-fold in about five years.

And so the -- to summarize, the reduction -- when you take mitigating action, the reduction can be delayed and it can be slow. And so when thinking about thresholds in a risk mitigation context, it is very important to realize that the threshold has to be set below what is unacceptable because you can't simply switch things off. And I will stop there.

DR. LONG: Thank you, Mark. Okay. The final word comes from Dr. David Bell. He is an Assistant to the Director for Antimicrobial Resistant at the National Center for Infectious Diseases at CDC. He is a specialist in pediatric infectious diseases in public health.

David Bell, M.D.

DR. BELL: Thank you. I am going to be able to shorten my remarks because I agree with virtually everything that Dr. Lipsitch has just said. CDC commends the FDA and Dr. Vose on developing this model. CDC believes that it reflects the available data well and we agree with the overall approach and the overall conclusions.

This analysis provides additional insight into the harm that fluoroquinolone use in poultry is currently causing to humans in the United States. The model is also a useful step for assessing what impact could result from more serious fluoroquinolone-resistant infections such as Salmonella.

We have some suggestions for minor adjustments that we will provide as follow-up. But one of them, for example, is to consider the harm caused to the 135,000 people who are estimated to acquire infections with Campylobacter and not be treated with antibiotics. And this refers to the increased length of illness, that we have emerging data to assess.

We would like to see if the model could be used more predictively to get some idea of the consequences for the future if current trends continue. In terms of fluoroquinolone resistance and Campylobacter in humans, it is increasing approximately two percent per year.

Fluoroquinolone use in humans is also increasing. And the impact of these two trends may also need to be considered. For example, the rate of fluoroquinolone treatment of 55 percent of the cases is probably going to rise. I want to connect that with a little clinical insight, if you will.

Fluoroquinolones are by far the best drug for the empiric treatment of bacterial gastroenteritis and its complications. This drug is oral. It is safe. It covers the spectrum of likely pathogens. And it really is the drug that all of us would want presenting with an infection that was thought to be a bacterial gastroenteritis or its complications.

The drug has not to date been used in children. That is primarily because in baby rabbits, it causes cartilage damage. However, the evolving collective thought in the pediatric infectious disease community based on studies and increased experience in certain unusual situations in which it has been given to children is that this is an effect in rabbits only, not in children particularly in short courses.

And it is quite possible that fluoroquinolone use will continue in adults and will begin in children. And so I think that I would just offer this to the modelers as something to consider in assessing the -- using this model, the trends that can be expected if no action is taken to mitigate the current hazard. Thank you.

DR. LONG: Thank you, Dr. Bell. Okay. I am going to stand up again. What I want to do is get an assessment of how many of you might want to have comments during the public comment period so that we can gage how much time we have for questions of the panel. Can I see a show of hands, who is planning on commenting during the public comment period?

(Show of hands.)

I see one. I see David is going to comment then, three, four, five. Okay. Okay. So I think what we can probably do if we were to limit those comments to about three minutes, then allowing a few more people might stand up, we can spend at least 15 minutes here if there are questions to address to the panel. You can step up to the microphone at this time.

(Away from microphone.)

DR. VOSE: --- have a point ---

DR. LONG: That would be great if David would clear up some points. Yes.

Questions/Comments for Panel

DR. VOSE: Thank you. I just want the rest of this discussion to progress with a few of these points clarified. Several people made a comment about change in pathogen load if you had a food product that changed in pathogen load, well, that would affect the risk. Well, I utterly agree with you. And from the very beginning, I was very conscious of that.

So there was a little mathematical technique I developed which I admit is not in the paper as you see it. And it is perhaps a little bit too mathematical for most of your tastes. But it allows us to make a reasonable approximation to the change in a pathogenic load at the point at which we are going to consistently measure.

So we can take that into account. And I totally agree that it is important to be able to do that, to have that facility.

A comment about Bayesian inference. Well, there was a comment about that one of the speakers believed that Bayesian inference should combine both expert opinion and available data. And, again, in a traditional Bayesian inference approach, that is exactly right. Of course, that first of all requires somebody to give an opinion. And you can appreciate that there would be a lot of rather different opinions.

So what we felt was a better approach was simply to use, as you rightly pointed out, an uninformed prior which meant that we base all of our assessment on data and none on expert opinion. Now, we could include expert opinion.

The comment you made that said that maybe that would increase the uncertainty, in fact, nearly always if you have a prior that is informed, that is not uniform, for example, well, actually your uncertainty decreases, your combined data, unless the data and the opinion violently disagree which is presumably rather unlikely.

But unless they do, then you would actually have a smaller range of uncertainty than we show at the moment. So in some ways, I appreciate the -- I have been a little bit overly cautious by assuming uninformed priors all the way through.

I also used an uninformed prior just because it is more equivalent to classical statistics where classical statistics do not take into account what people believe, just what the data tells you. So for those of you who are more classically trained, you would have less of a problem with the analysis.

Could -- a very good point was about making model predictions of fluoroquinolone resistance trend. And the way this model is set up, you can do a separate model which is trying to predict what the fluoroquinolone resistance will be doing in the future using trends perhaps from other countries or perhaps what one believes is going to occur in a few years of fluoroquinolones. And you could simply have to put that fluoroquinolone prevalence within the Campylobacter that you mentioned might be there in the future.

Now, there was one other thing, a misunderstanding of what the point of this Pmax was about. It wasn't about an individual shed being tested. It was about the population as a whole. So you wouldn't grab somebody and say, "Oh, look, you have gone over Pmax. You are out of here", sort of thing. It would be all embracing for the whole U.S. which hopefully would dampen down the, you know, any sort of very sensationalist reaction that one might have. Thank you very much.

DR. LONG: Thanks, David. Okay. So we addressing comments to the panel now. Go ahead.

MR. : I was just wondering, it was brought up earlier that there has been a rather dramatic increase in the amount of chicken consumed over the last few years without a corresponding increase in the number of human Campylobacteriosis cases. And I was wondering of the panel can comment on what they think are the reasons.

I can think of a couple. One, that a lot of it, as was brought earlier, is in the form of Dave's spicy chicken sandwich and stuff like that that is presumably a low risk vehicle. Also, that perhaps consumers are increasingly aware of contamination and are preventing cross-contamination and have better cooking practices, or that perhaps industry is making a better product.

DR. LONG: I am not sure that we have any consumption experts up here today. Are you pointing to one in the audience? But does anybody want to address that? Okay. Next at the microphone.

MR. : I was concerned about a statement by Louise that she thought that we would have to re-think this whole process again and it would be quite laborious to do other drug-bug combinations. And I would be interested in either David's comment on that or comments from everybody else on the panel because of the obviously time delay that would be necessary to address a whole spectrum of concerns.

DR. KELLY: I will stand up again. What I was thinking on here was really that not to assume that you can use exactly the same format within -- for another drug-pathogen combination and simply put in new numbers. You have to have some consideration into different processes.

MR. : I would agree that we would obviously have to put in the new data. But for any other food-borne pathogen, Salmonella or Yersinia, it could be -- this model would hold I think for Yersinia and for Campylobacter.

DR. KELLY: But for other --

MR. : E. coli 0157.

DR. KELLY: -- non-C. enterococci that are food-borne.

MR. : Well, no, no. Not non. But food-borne zoonite pathogens, I don't think you need to rethink the whole process.

DR. KELLY: So you have to consider then what the actual pathogen is that you are looking at.

MR. : Absolutely.

DR. LONG: Over here. Is there a microphone? Okay.

MR. WOOD: Hi, I am Richard Wood with FACT, Food Animal Concerns Trust. When I was looking at the risk assessment fairly quickly and then also thinking about the

Framework Document and what kinds of things were a part of that document in terms of the data, was industry use of fluoroquinolones factored in to the risk assessment? And if it was not, would that be useful information to have in terms of the pharmaceutical sales and actual use by the industry?

I know that we have heard here in the session people speak to the amount of fluoroquinolone use on poultry farms. But I was wondering if that was a part of the analysis and if it was or was not, if that would be a helpful part to have. Certainly, the slide we saw on the Finnish use of erythromycin, it looked like that was a helpful part of that kind of an analysis. And I was wondering if the same would be true here.

DR. LONG: David, do you want to address that?

DR. VOSE: First of all, we assumed, of course, that fluoroquinolone use in poultry is resulting in fluoroquinolone-resistant Campylobacter. So from that point of view, we are making that assumptive connection.

No, we don't look at the volume of fluoroquinolone used because one may change practices in how fluoroquinolone is administered. For example, if -- at the moment, fluoroquinolone, I have no idea. But if it is administered in water every time a chicken sneezes, then that would be perhaps an excessive use of fluoroquinolone.

But, on the other hand, if it used in an entirely scenario or if it is used without deep litter bedding, lah, lah, lah, lah, there are all sorts of different ways in which one may properly or improperly use the fluoroquinolone. So I didn't really want to get into that whole issue.

We are simply looking -- assuming the causal link, we are looking at the size of the effect. Now, maybe there was a just a few people who were using, but not using it very well or maybe a great deal of people are using, but are using it very well. Ultimately, if it comes down to the same thing, it makes no difference to us.

DR. LONG: Other questions?

DR. SMITH: Yes, I just wanted to address Dr. Singer's concern about his perceived lack of resolution of our molecular subtyping methods that are in the New England Journal article. It is true, subtyping methods for Campylobacter are not very advanced. We haven't found a good method, maybe because, you know, chicken carcasses can have different subtypes. That is probably one reason why we don't find them very useful.

But in our case, the resolution is there. I mean, we found quite a bit of variability. And I don't think we need to be overly concerned that molecular subtypes were found in the United States and in people returning from foreign travel. For one thing, I think just because somebody had a history of foreign travel doesn't necessarily mean they could have acquired their infection in this country.

And secondly, you know, what is to say that we don't have some subtypes in common, some clones in common between the United States and especially places like Mexico. And so I don't think we should be concerned about the fact that there is the same subtypes in different places like that.

What you didn't mention is that in the paper -- and I would be glad to show that to anybody -- is that we did have a very strong statistically significant association between having a domestically acquired resistant strain that was also found in poultry as compared to foreign travelers with a resistant strain and also as compared with domestically acquired resistant cases. And so I wouldn't necessarily discount the utility of the method just based on that point.

DR. SINGER: Yes. Actually, my intention wasn't to in any way make a negative play on the methodology of the paper, etcetera. It was just to bring out the point that especially like in the case of trace-backs or whatever, there are potential problems.

And, I mean, one is that where do we even look.

You know, I mean, the paper focused on chickens. But if we were to look at other sources, would we have also found the same subtypes in other sources? And if so, then how do you start making that linkage between what was the source of that resistant isolate.

So all the point was meant to say is that assigning a causal link because of similarities to me is a difficult endeavor. The use of a statistic in that case of an odds ratio to me is difficult, as well, because sampling differences in the way you might culture products in the U.S. versus people returning -- and people in the U.S. versus the cases in where they were exposed international potentially, I agree with you. They could have been exposed in the U.S. They had a history of travel. But it was just to bring up that issue.

DR. SMITH: All right. And other people have asked me about that, molecular subtyping, as well. I mean, that is in our paper. And because we used fluoroquinolone-sensitive Campylobacter cases as controls, you know, we weren't able to show a link to poultry in any other way. Both groups had very high poultry consumption rates.

But we could argue about the utility of the -- of using the statistical test on there I guess. But I guess we feel it is very appropriate. And it is not only that. It is in the context of the fact that we know poultry is the major source of Campylobacter for humans. We know up to that point, poultry was the only animal in this country that -- food animal in this country that fluoroquinolones were used on.

And so you definitely have to look at it in the broader context of all the ecological data. So I just wanted to clarify.

DR. LONG: Okay. We have time for one more question to the panel. You are it.

MS. : Hi. I have a question for David Vose and CVM. Should the rate of resistance development in target pathogens for which the fluoroquinolones are being used in the poultry be factored into the model or was some thought given to that? For example, this rate will impact veterinary usage and that will also impact humans' resistance rate in the future.

DR. LONG: Okay. And into the microphone, too.

MS. : I'm sorry.

DR. LONG: Maybe David could come up so she can look at you at the same time. Okay.

(Laughter.)

MS. : I will repeat it. This is question for the modelers of CVM. Should the rate of development of resistance in the target pathogens for which fluoroquinolones are being used in poultry be factored into the model? In other words, the rate or the amount of usage in veterinary medicine is going to -- if that lowers because resistance has gone so high in the target pathogen, it is going to affect up or down the rate of resistance development in humans.

DR. HOLLINGER: First of all, the rate of development of resistance in the target pathogen issue is more an efficacy issue. So that looking at it from that perspective, we really did not. As far as looking at drug use specifically which is a little bit separate and trying to tie that into the model, I think it is from my perspective feasible to tie it into the model should we have better information at this point.

We don't have adequately detailed information, drug use information, to try and tie it into the model. And then we would also then need to model the secondary effects of contamination during the chiller and also maybe re-use of litter issues, as well. So I think that that might be a later stage or a later step or something that could be discussed about tying drug use information into a model like this.

DR. LONG: Thank you, Kathy. I want to thank the panel for their excellent summaries of the risk assessment and allow them now to step back down. We are going to open up the --

(Applause.)

PUBLIC COMMENT PERIOD

DR. FEDORKA-CRAY: I think that I have some idea of the amount of time that it took the people at CVM to put this together. And I really think that we do owe those people our thanks and a round of applause.

(Applause.)

DR. LONG: Jim Heslin who is our FDA Training Officer is going to join me up here on the stage to facilitate the public comment period. And Dr. Sundlof is also coming up, so you can address your comments to him.

DR. HESLIN: Thank you. I am a little hesitant to say this, but good evening. I took a look outside and it is dark out there. We have come to the end of a long day. But I think it is an important part. It is an opportunity for you all to provide your comments on perspectives, on the issues that were presented and discussed here today.

I know Dr. Thompson and others felt this was an important component, that they wanted to hear from you. So this shift now is to FDA as the listener, to hear your comments. It is not a forum for debate or protracted discussion. But we are here to listen.

A couple of ground rules. When you come forward to the microphone, I would appreciate it if you would identify yourself and your organization. We don't have a lot of time and I am not sure how many people are going to be speaking. But I would ask that only one person from each organization, if there are multiple representatives, would speak for the organization.

We are going to start by limiting comments to about three minutes. If there is more time at the end, we can always come back or you can always submit comments in writing. At about two and a half minutes, if I can figure out the clock, I am going to let you know that you have about half a minute left. At that point, if anyone else wants to speak, that is a cue to move to the microphone so that we don't lose time in the transition.

Now, this is the important piece. When the three minutes is up, you are supposed to tap the person on the shoulder and tell them to move on. Okay?

(Laughter.)

Because I don't like to shut people down. I will, but I don't like to. Okay. Thank you for your cooperation in advance. And we will go ahead and get started. Who would like to begin? Would you like to step forward to the microphone, please.

DR. SHRYOCK: Tom Shryock representing the NCCLS, Veterinary Antimicrobial Susceptibility Testing Committee. I probably took 30 seconds there. I just wanted to add an assumption I think that should be included here. And that is that the breakpoints that are used to characterize an isolate as fluoroquinolone-resistant need to be assumed -- are assumed to be valid in terms of the clinical outcome.

At this point, just to reiterate from this morning's talk, I am unaware of data that has really matched MICs specifically to clinical outcomes with regard to Campylobacter. And I think that sort of data, there has been assumptions made on that. And I think it would be worthwhile to try to piece together whatever available data there is or to secure sponsored data along those lines as appropriate.

Since we have talked about gastroenteritis being treated by fluoroquinolones as well as systemic disease, there are two different pharmacologic patterns that could be involved which could affect where that breakpoint is set.

And then finally, the breakpoint itself may not be indicative of a resistance mechanism. It may be due to the pharmacology which is the achievable drug level exceeding the MIC. So there are some factors that go into what really determines a fluoroquinolone isolate. Thank you.

DR. HESLIN: Thank you.

MS. LIEBERMAN: Hi. I am Patty Lieberman from the Center for Science in the Public Interest. We represent a million consumers in the United States and Canada. And I guess I am part of the risk communication team.

Basically, we feel that FDA's responsibility in regulating animal drugs is to assure the reasonable certainty of no harm to human health due to the use of antibiotics in livestock. But CVM's own risk assessment shows harm to about 5,000 people. Therefore, we think that the fluoroquinolone approval in poultry which never should have been allowed should be revoked.

Consumers should not have to continue to be guinea pigs in this regulatory experiment. What level of harm will result in CVM action? Is it going to take 10,000 more severe illnesses? Will it take death? Or will CVM continue to not do anything in regulation by redefining what the word, "harm", means and looking for a different legal standard to apply?

Now, about using the similar risk assessments for other antibiotics and pathogens, the concern is that using a risk assessment like this for future decisions is predicated upon waiting for resistance to develop, for being transferred to people, and for causing significant human health harm before action could possibly occur.

Instead, we need a preventive strategy to apply to new drugs considered for approval that would monitor changes in susceptibility in livestock before they have a human clinical consequence. Finally, the entire process which has been initiated by the FDA is clearly very slow and laborious and controversial. And it is too slow to deal with the public health risk.

We can endlessly debate the framework, the risk assessment, the legal standard and still do nothing. Meanwhile, consumers are being harmed. Thanks.

DR. HESLIN: Thank you. Is there anyone -- yes, over here.

MR. CONDON: Robert Condon. Just a couple of issues. I want to thank you. You have done a good job. There is a lot of details in there. Don't get caught up in the details and don't put too much emphasis on certain point values.

The issue I would like to bring up is when you look at this, look at it as a probability of risk given the exposure. That is the bias that occurs in a lot of risk estimates and a lot of risk assessments. Like this data has the bias in it, it assumes 100 percent of the population is exposed. Therefore, those risk values you have under-estimate the true population risk to those that are exposed to the hazard.

An example, if I told you only five people were killed bungee jumping last year, you could say, well, that is way less than one million; that is one in 50 million. So bungee jumping should pretty safe. Now, if I told you there was only 20 people that went bungee jumping, you would probably have a different idea of that.

But when you spread that risk across a whole population, you end up with a bias estimate. You can get at this -- USDA has some very good intake data. I mean, they can tell you how much processed chicken, how much cooked chicken each individual had; how many people had chicken down to -- the detail that they go to is they can tell you how many people had raccoon. That is in the database.

So you can get -- to get the exposure, you can get a pretty good handle on that. The data is available. One of the things that I have a hard time reconciling here with the data is the paper on the seasonal variation. You have got about a four-fold difference in incidence seasonally due to cases. I doubt whether your chicken consumption is four-fold -- varies four-fold seasonally.

If it is truly 50 percent exposure from causing the Campylobacter, if 50 percent is coming from chicken, you should be able to track the chicken consumption in those incidence of cases fairly well. I don't know if that is in the data, whether you could do it.

I doubt it, when you've got a four-fold difference in the number of cases you are going to see a four-fold increase in the consumption of chicken. You might be able to look at that from USDA data. But I think that is something to look at to evaluate those estimates.

DR. HESLIN: Thirty seconds.

MR. CONDON: Okay. Thank you. So that is one of the things. Look at the USDA consumption data. The other thing I would like to bring up is you have got to look at the quality of the data. And just because you have a number that says it is six and it's just -- like this risk assessment -- you are probably going to see tonight on TV, 70 percent of the Campylobacter cases come from poultry.

I mean, that is a value. I mean, people pick up on the single values. They take on an intrinsic worth. I mean, I lived for years with the value of two parts per billion being safe for DES. It just -- there was no good basis, but it becomes entrenched.

And because a value is published doesn't mean it is accurate or worthwhile. And I think you need to look at little bit more at that at your own -- some of the data that CVM had collected. There is questions on some of that data. Take a look at those studies and really spend a little time looking at the studies to see whether they are worth it. Just because you've got a value doesn't mean it is better than no value.

DR. HESLIN: Thank you. Next.

DR. ANGULO: Fred Angulo, Food-borne and Diarrheal Diseases Branch, Center for Disease Control and Prevention. We agree that there is a marked seasonality of

Campylobacter. The seasonality of human sporadic illness actually matches quite closely to the seasonality of Campylobacter contamination found in grocery stores and also found on farms.

We also -- there also though -- seasonality is not all explained by contamination rates. There are seasonality "mishandling" characteristics such as increased outdoor barbecuing and other factors in the kitchen that might explain seasonality.

But the seasonality is fully -- the seasonality affects are fully understood in terms of the current understanding of the epidemiology. And the conclusion is still the same, that the predominant source of Campylobacter is poultry.

There also was questions raised about the MICs of fluoroquinolone resistance and Campylobacter. Campylobacter is remarkable bacteria in that a single point mutation in the gyrase causes the MICs to be at the highest detectable or measurable level. Wherever you set the breakpoint, they are always at that level. It is not a breakpoint set point. They are all at the highest level of the MIC.

And we have done -- we have looked at Campylobacter isolates from humans that are fluoroquinolone-resistant and find the consistent base permutation and correlating the biological resistance -- correlating the laboratory resistance with that mutation.

So reiterate a point made by Dr. Bell, CDC would like to commend CVM for undertaking this risk assessment. The risk assessment clearly demonstrates that the use of fluoroquinolones in chickens is now causing harm in humans in the United States.

This harm is not trivial. Harm to people now may be somewhat greater than estimated. Harm is likely to increase each year. Steps to mitigate the harm are needed now.

A meeting to plan these steps should be held within the next three months. In particular, we need to establish fluoroquinolone-resistant threshold in Campylobacter and we need to establish a timely procedure for drug withdrawal in the event the resistance threshold has been crossed.

DR. HESLIN: Thank you. Yes?

MS. BUTLER: Good afternoon. I am Kelly Butler with the Bureau of Veterinary Drugs from Health Canada. And I would certainly like to commend the Center for Veterinary Medicine of the Food and Drug organization of the United States. It is especially gratifying to have a tool that seems to be a tool that will be used for all food-borne pathogens and resistance.

I think some people that I have spoken to here have found that their -- they feel that chicken are being targeted or a particular bug is being targeted. But in terms of regulators who have to make decisions, we need a tool based on science.

Doug Powell earlier today said the alternative is astrology. We are scientists here and we need to make decisions based on science.

I was especially pleased to have two mathematicians who could actually speak English and explain issues to us because as scientists, we know, too, that we end up speaking a language that many people can't understand. But when we speak to the public, which is my job as a regulator and the CVM's job, as well, we need to be able to speak English to communicate the risk.

And I think this represents a tool that we can use, that we can make decisions based upon using this tool. A small issue, I must say, too -- and I am trying to explain this issue of antimicrobial resistance to policy-maker. I am a policy person and a scientists, a published scientist. Some of the issues that we need to make clear are things like this debate or comments on the seasonality.

It is not just chicken that people eat and they get microbes I explain to other policy people. The other piece is the chickens that are in the grocery store on the little turn-around. And that contaminates other vegetables

-- or vegetables that the vegetarians may eat.

And additionally, poultry manure, swine manure, all sorts of manure are used in vegetables. So this issue isn't just one bug, one species. There are a lot of issues to look at. And I think this tool represents an excellent start. Thank you very much.

DR. HESLIN: Thank you. Yes, sir?

MR. BIOWATER: Robin Biowater, Consultant to Pfizer Animal Health. I would come back to this word, "harm." And I think it is debateable still what degree of harm can really be hung under fluoroquinolone use in poultry. And, indeed, that is what we are here for today.

But I think we shouldn't forget that the harm from Campylobacter infection in man is not the harm predominantly and overwhelming -- not the harm due to the resistance to fluoroquinolone, whether through treatment or increased virulence.

The harm from Campylobacter is the shear volume of cases, the shear prevalence of the disease and the number of people who suffer from it. And we should keep that in mind. And that should be the main target. And obviously, we should make any other targets we can identify at the same time.

I would like to just make a brief comment on the model which has I think been a very interesting exercise.

But I, like Louise Kelly, I am concerned that the idea can be easily applied elsewhere will firstly fall down because other organisms don't behave in the same way as Campylobacter and in particular because for other organisms and other connections, we are going to have a great deal of difficulty finding as much data to support the model as has been found for this one.

And unfortunately, I am afraid the extrapolation will be much more difficult than I think Fred implied, at least for food-borne organisms. Thank you.

DR. HESLIN: Thank you. Any other comments? And the race is on.

(Laughter.)

DR. CLOPP: My name is Buzz Clopp. I am a veterinarian. I work in the chicken industry and have for a number of years. And my intention is not to stand here and ridicule the model and the development of the model. I think it has been a lot of work. It has been very well done.

But I do have to say that, you know, I have some concerns about. And some people have already said that they don't believe that these are concerns. But I guess I have to say that I don't agree. The number one concern being the -- to somehow factor in the level of treatment that is done in the field.

I think as I understand this model, the way it is done right now, you are making a direct assumption between resistant Campylobacter on the carcass and chickens. Well, guess what. There is another factor in there. And it was mentioned about the environment and about manure going on fields and going to vegetables.

There is a huge amount that we obviously don't know about the epidemiology of Campylobacter. Does Campylobacter go from chickens to people? I suspect it does. No question.

Does it go from people to chickens? I suspect it does because we have -- chicken houses are not isolated vehicles. Processing plants are not isolated vehicles. There is cross-contamination and it goes both ways.

Now, my intention is not to stand here and to be defensive. As a person working in this industry, it is our intention to make a quality food product that people can not only enjoy tasting, not only get good nutrition from it, but feel good when you eat it. And obviously, people do.

And there is a lot of circumstantial aspects to all this. And I don't disagree with public health. You know, hey, I am a human obviously. I have children. I have grandchildren, the whole works. But, you know, slow yourselves down a little bit and think.

You know, number one is chicken consumption is increasing. But it doesn't appear that the level of all this is increasing at the same rate. You know, what else is going on? You know, study, but please don't overreact. And I am going to sit down.

As an industry, agriculture and food production in this country is under an assault from many, many, many factors. And what people had better start to realize is -- and the inference was made this morning about chicken at $1.49 a pound. That is not the same price per pound as what you bought chicken 20 years ago.

Twenty years ago, you were buying predominantly a whole chicken for probably 35 cents a pound. The average consumer today does not want to buy a whole chicken. They want to buy a boneless breast or they want to buy de-boned thighs or they want to buy buffalo wings, all of this. And that is why you see these costs going up.

So all I am saying is, you know, we need to move forward with this because it is an issue. But slow down and keep a little bit of science on the whole thing because there is a lot of factors involved in this.

DR. HESLIN: Thank you.

DR. KRISHINSKY: My name is Dr. Elizabeth Krishinsky. I am with Wompler Foods. I am also with the broiler industry. And I am not going to philosophize anymore. I just have a simple question.

I think the model itself even -- I congratulate you on the model because even I can understand how it was put together and I am not an epidemiologist. I have had some statistics, but it is not my area.

And I can clearly see how you have modeled the clinical progression of the disease and extrapolated backwards to the number of people in the population that are affected with Campylobacter illness in a year and then divided by that the consumption of poultry.

But to me, I think we have overstated what the consequence or what implications this has for fluoroquinolone use in poultry. There is nothing in the model -- it is a little bit of the "emperor's clothing" analogy.

There is nothing in the model that addresses fluoroquinolone use at all. It starts with the assumption that the use of fluoroquinolones causes resistance -- fluoroquinolone-resistant Campylobacter on chicken.

So the model says if Campylobacter from chicken have fluoroquinolone resistance, then what is the impact on human health. And I agree, it is an excellent model for that. There may be some people that quibble with the data, etcetera. But it is very simple. It is easy to understand. And even the statistics are easy to follow.

My question to you is how can you comfortably and really with good conscience extrapolate and draw any conclusions or suggest any interventions on the live side and tie this to fluoroquinolone use when there is nothing in the model that at all addresses that. Thank you.

DR. HESLIN: Thank you. Yes?

MR. : I guess I would be remiss if the Animal Health Institute didn't make some comments at this meeting today. First of all, let me congratulate CVM on undertaking a very difficult and complex task.

AHI has certainly supported the idea of risk assessment as a way to get a handle on this whole area of antibiotic resistance for a number of years now. And we appreciate the difficult job that has been undertaken in trying to tackle this problem.

Now, we haven't obviously had this risk assessment for very long. So we can't obviously give you very many detailed comments today. We will be providing more detailed comments in writing, of course, in the future. But let me just make some general comments on the model itself and then touch on some of the assumptions.

In a way, I guess I wouldn't characterize this as a true risk assessment. I think for what it was intended for was really a retrospective case prevalence estimate based on the FoodNet data. So then we back calculated some probabilities. But this is really based on what has occurred in the past, extrapolating to what my occur in the future.

A true risk assessment in my mind would factor in the consumption aspect of poultry, what happens in the process through the handling and cooking, estimation of the infectious dose and what cooking and handling procedures can do to reduce that risk as a prospective estimate of what the risk to the population could be.

So I think there is a little bit of difference here between this risk assessment and what I would view as a true prospective risk assessment. So that would be the first comment I would make.

On the assumptions, there is one assumption that is in the document that states that the level of resistance -- or the level of risk is assumed to be the same as it was in the 1980s -- it is the same today as it was in the 1980s.

And I think that is probably a fairly flawed assumption if you look at what has happened in the 1990s with regard to the changes in meat inspection, the implementation of HACCP, the implementation of Salmonella performance standards, safe meat and poultry handling labels which is on every single package of raw meat and poultry that is in the supermarket case today telling the consumer there can be potential pathogenic organisms in the product, that they must handle it, they must cook it properly and they must take proper precautions.

There has been an incredible amount of money put into the President's Food Safety Initiative. The FDA has their own "Bite Bac" program which I think is being considered a success. So what I am saying is that you cannot assume that the risk from the 1980s is the same as it is today. And I think that assumption is one that really needs to be addressed in the model.

I won't make any further comments other than, again, I appreciate the opportunity to comment on this today. We will be having more in-depth remarks in writing on this particular process.

One other thing I would like to close with before I forget is that, you know, we came here today -- the industry I think came here today expecting maybe a little more progression in where we were headed with this whole thing. We do support the idea of risk assessment. But we are afraid that this quite hasn't connected the dots to our satisfaction. Okay.

What do we do from here? Exactly where does the industry go from here and how does the industry deal with the drug approval process? I know it is a complex issue, Steve, and I understand you are trying to work through it. But I guess we expected a little more definite program to be laid out for us today. Thank you.

DR. HESLIN: Thank you. Yes?

MR. WAGES: I am Dennis Wages. I am a teacher at the Veterinary School at North Carolina State University in poultry medicine. And, Steve, as always, your group has done an excellent job putting this model risk assessment together. The one thing I would like to emphasize is the pathogen load and the number of organisms on these carcasses.

From my standpoint, looking at mitigation intervention strategies from our end in the industry, you are, are the affecting numbers either by pH adjustment in chillers, the cold pasteurization, irradiation, etcetera, etcetera, how that is going to affect public health impact by reducing numbers.

And that load that is on that carcass, because we know the infection is a result of some kind of a dose relation there, that is going to be important for us to try to go in either through research or whatever and intervene to try to decrease numbers, if not eliminate numbers, of bacteria on the carcass.

So I think the pathogen load on those carcasses are a very important tool for the mitigation intervention strategies to try to employ -- to prevent the contamination from occurring at all in the poultry.

DR. HESLIN: Thank you. Is there anyone else? Okay. Keeping with the pledge that we would be out by 6:00, we are pretty close to it. So thank you very much and see you all tomorrow.

(Applause.)

(Whereupon, at 5:50 p.m. on Thursday, December 9, 1999, the Workshop on Risk Assessment and the Establishment of Thresholds was recessed, to reconvene at 8:30 a.m. on Friday, December 10, 1999.)